ESMO Open Cancer Horizons

PIK3CA mutation inhibition in hormone receptor-positive breast cancer: time has come

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To cite: De Mattos-Arruda L. *PIK3CA* mutation inhibition in hormone receptor-positive breast cancer: time has come. *ESMO Open* 2020;**5**:e000890. doi:10.1136/esmoopen-2020-000890

Received 2 July 2020
Accepted 4 July 2020

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The phosphatidylinositol-3-kinase (PI3K) pathway is mutated and aberrantly activated in breast and other cancers and plays a key role in cancer cell proliferation and survival.[1 2] The PI3K pathway is deregulated through a variety of mechanisms, including mutation or amplification of PI3K, loss or inactivation of the tumour suppressor phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*), as well as activation of tyrosine kinase growth factor receptors or oncogenes upstream of PI3K.[3 4]

Activating mutations in *PIK3CA*, the gene encoding the alpha isoform (p110 α) catalytic subunit of PI3K, is present in up to 40% of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancers[5 6] and represents a molecular target to personalise therapy of selected patients with breast cancer.[2]

Standard of care therapy for advanced HR-positive/HER2-negative breast cancers consists on endocrine therapy with or without the use of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors.[7] Therapy-resistance inevitably occurs in the majority of patients. The rationale of combining PI3K inhibitors and endocrine therapy is to synergistically inhibit both the PI3K and ER pathways.[8]

Initial trials of pan-PI3K inhibitors plus endocrine therapy for patients with advanced breast cancer showed modest benefit with high rates of toxicity limiting their clinical drug development.[9–11] Selective isoform-specific PI3K inhibitors, such as an α-specific PI3K inhibitor, have subsequently revealed activity with less toxicity.[12 13] The phase III SOLAR-1 (Clinical Studies of Alpelisib in Breast Cancer 1) trial investigated the efficacy and safety of alpelisib, a α-specific class-I PI3Kinhibitor, plus fulvestrant versus placebo plus fulvestrant in patients with metastatic HR-positive/HER2-negative breast cancer who had received endocrine therapy beforehand.[14] About 85.6% of patients had endocrine-resistance disease.

Alpelisib plus fulvestrant met its the primary endpoint by significantly extending progression-free survival (PFS) versus placebo plus fulvestrant in the 341 patients of PIK3CA-mutant cohort at a median duration of follow-up of 20 months (HR 0.65; 95% CI 0.50 to 0.85; p=0.00065; median 11.0 vs 5.7 months). Overall response (26.6 vs 12.8%) and clinical benefit (61.5 vs 45.3%) also favoured alpelisib plus fulvestrant arm. Response rates in the mutation cohort with measurable disease were doubled (35.7% vs 16.2%; p=0.0002). In contrast, in the *PIK3CA* wild type cohort (n=231), alpelisib only modestly extended PFS (7.4 vs 5.6 months; HR 0.85; 95% CI 0.58 to 1.25). The most frequent adverse events in the alpelisib arm were increased incidences of hyperglycaemia, an on-target effect related with the activity of alpelisib and diarrhoea, nausea and rash compared with the placebo arm.[14]

In a subgroup analyses from the SOLAR-1 trial,[15] a statistically significant benefit in PFS was also observed for alpelisib in patients with PIK3CA-mutant detected in the plasma cell-free tumour DNA (ctDNA), assessed as liquid biopsy (10.9 vs 3.6 months; HR 0.55; 95% CI 0.39 to 0.79; p=0.0005).[15–17] The benefit of administering alpelisib was consistent across patient's subgroups, including patients that had previously received neoadjuvant and adjuvant therapies, those receiving second-line therapy and patients that had less than three metastatic sites affected.

These data suggest that *PIK3CA* mutations are relevant therapeutic targets in advanced or metastatic HR-positive/HER2-negative breast cancers with PI3K pathway dependence. On 28 May 2020, the European Medicine Agency granted marketing authorisation for alpelisib in combination with fulvestrant for the treatment of postmenopausal women and men, with HR-positive/HER2-negative,

locally advanced or metastatic breast cancer with a *PIK3CA* mutation after disease progression following endocrine therapy as monotherapy.

The approval of alpelisib in combination with fulvestrant for PIK3CA-mutant endocrine resistant patients with breast cancer is an important step towards Precision Medicine. However, this progress comes with a few challenges.

First, the SOLAR-1 trial enrolled very few patients pretreated with the current first-line standard therapy—a small number of PIK3CA-mutant HR-positive/HER2-negative patients received prior therapy with CDK4/6 inhibitors (5.9%, 20 patients).[15] For patients who have PIK3CA -mutant disease and progress on a CDK4/6 inhibitor-based therapy, alpelisib plus fulvestrant is a treatment option, and there is emerging clinical data available.[18] In the phase 2, non-comparative, 3-cohort BYLieve trial (ClinicalTrials.gov number, NCT03056755,[18] alpelisib plus endocrine therapy (fulvestrant or letrozole) is administered to patients with advanced *PIK3CA*-mutant HR-positive/HER2-negative breast cancers whose disease progressed on or after CDK4/6 inhibitor plus endocrine therapy. The results of one of the three cohorts (cohort A) of the BYLieve trial, in which patients with prior CDK4/6 inhibitor plus aromatase inhibitor received alpelisib plus fulvestrant, showed that 50.4% of patients were alive without progressive disease at 6 months. Median PFS was 7.3 months.[18]

In addition, although the SOLAR-1 is a well-designed study, it does not answer a question that arises in the real life: would fulvestrant single agent be the choice as second-line endocrine therapy, knowing the efficacy of endocrine therapy plus everolimus, that works regardless of *PIK3CA* status? Fulvestrant plus alpelisib versus fulvestrant plus everolimus is yet to be compared.

Second, the source of genetic material (tumour tissue and/or plasma ctDNA) and the technology for profiling *PIK3CA* mutation is undefined yet. The SOLAR-1 and BYLieve trials[14 18] profiled *PIK3CA* gene by polymerase-chain-reaction analysis of mutation hotspots in exons 7, 9 and 20. Patients could be profiled and selected for therapy if presented a *PIK3CA* mutation in tumour tissue specimens[14 18] and/or in ctDNA isolated from plasma specimens.[15] The use of a liquid biopsy would be adequate to select patients for therapy. A liquid biopsy has the advantage of being a non-invasive, rapid, real-time assay and can be used to profile and serially monitor breast cancer patient's progress.[16 19] It may reveal each patient with breast cancer repertoire of mutations as an up-to-the-minute tool, reflecting the disease status and heterogeneity.[20] In addition, it may broaden the number of targetable biomarkers that can be used to develop a personalised therapeutic approach for each patient.

Third, there is a number of single gene tests and multigene panels that differ across companies and academic institutions.[21 22] The best strategy is not standardised yet. Currently, next-generation DNA sequencing technology offers simultaneous testing for multiple genes, which has pros and cons in terms of turnaround time and possibility to detect *PIK3CA* and other concomitant mutations that could be associated with either increased sensitivity[23] or resistance to PI3Kα inhibitors.[12 24 25] Double *PIK3CA* mutations in cis (ie, on the same allele) than single mutations have shown increased sensitivity to PI3Kα inhibitors.[23] The hotspot mutation *PIK3CA* H1047R seemed to be associated with higher clinical benefit from alpelisib compared with helical domain mutations in a phase 1 trial, a finding not confirmed in other studies.[12] Patients with PIK3CA mutations and concomitant alterations in *TP53, KRAS* or *FGFR1* did not benefit from alpelisib.[12] Concomitant mutations in the mitogen activated protein kinase pathway may mediate therapy resistance in patients having *PIK3CA* mutation.[6 24]

In conclusion, *PIK3CA* mutations represent a target to guide therapy in endocrine resistance HR-positive/HER2-negative breast cancer. The role of administering alpelisib after CDK4/6 inhibitor-based therapy should be consolidated. Patients could take advantage of a liquid biopsy to uncover *PIK3CA* mutation for alpelisib eligibility if they are unfit or are otherwise unable to provide a tumour specimen. Although some PIK3CA-mutant patients derived prolonged clinical benefit with α-specific class-I PI3Kinhibitor, not all patients with *PIK3CA* mutations have similar benefit from PI3K inhibitors. Also, a small fraction of patients without *PIK3CA* hotspot mutations respond to PI3K inhibitors. Clinical trials are ongoing to evaluate new combinations of PI3K-targeted agents as well the role of other genomic alterations (eg, *PIK3CA* amplifications, *PIK3R1* mutations) to better select and monitor patients under therapy.[3 26 27] Biomarkers of secondary resistance to PI3Kα inhibitors are should also be identified.

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Acknowledgements The author is grateful to Dr Miguel Martin for critically reading this manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests LDM-A has received honoraria for participation in a speaker's bureau/consultancy from Roche, and reports research collaboration and support from NanoString Technologies.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

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