Targeting PI3KCA pathway to improve patient outcomes in hormone receptor-positive breast cancer: a worthy 20-year wager?

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From the initial preclinical discovery of the biology of the PI3K pathway and its implication in cancer, to alpelisib, the first Food and Drug Administration (FDA)-approved PI3K inhibitor in breast cancer (based on the phase III SOLAR-1 trial, NCT02437318 [1, 2]), the scientific community has invested almost 20 years’ research into the PI3KCA pathway. Whether this body of work should be considered a little or a lot of biology, the past two decades have taught us a lot about PI3K and the promise of its blockade in patients.

Our main goals when developing novel anticancer medicines are always to extend patient survival and improve quality of life. Regarding duration of survival, the latest female breast cancer statistics report 5-year relative survival rates up to 90% for all stages [3]. Seeking out new therapeutic options that enable patients to live longer—and as well as possible—is crucial, since individuals with metastatic breast cancer may live with their disease for many years.

The four articles published in this supplement offer a rigorous review of the role and relevance of the PI3K pathway. Vasan et al. delve into hormone receptor (HR)-positive breast cancer and discuss the alterations described in the literature (PI3KCA mutations or amplifications, PTEN loss/mutant and AKT mutations), the cross talk existing between PI3K and ER, and the proposed mechanisms of resistance to therapy. In their exhaustive compilation of trial results and associated biomarkers, Brandao et al. examine those markers that promise prediction of benefit or resistance to this therapy, alone or in combination with other agents. Finally, Verret et al. focus on the prognosis that PI3K alterations may confer depending on disease setting and elegantly summarize the reported efficacy of pan-PI3K or specific PI3K inhibitors in the clinic.

These equally comprehensive reviews also try to tackle some of the many unresolved questions in this field. At which level is it best to target this pathway? A plethora of drugs has been tested in the clinical setting in phase I, II and III trials, adopting different approaches to more effectively block the pathway in different ways, including PI3K-mTOR inhibitors, pan-PI3K inhibitors and selective PI3K inhibitors. Myriad combinations supported by robust preclinical rationales have been tested in reversing well-described mechanisms of resistance. To date, only the selective PI3K-alpha inhibitor, alpelisib (PIQRAY™, Novartis Pharmaceuticals Corporation), has been granted FDA approval in combination with fulvestrant for postmenopausal women and men with HR-positive, HER2-negative, PI3KCA-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen [1, 3].

Other drugs have either failed to demonstrate enough activity or the toxicity profile has not supported further clinical development. Noteworthy is the recent discontinuation in later stage clinical development of taselisib after the results of the SANDPIPER phase III study (NCT02340221) [4]. While it was a statistically significantly positive trial, showing an increase in progression-free survival, the benefit was not reported as clinically relevant when factoring in toxicity. This deterred Roche from filing for regulatory approval. Extensive details of the most relevant clinical trials results on activity and toxicity are included in the three manuscripts. Better understanding and more effective management of emerging PI3K pathway inhibitor-specific toxicities, such as hyperglycemia or rash, are required to maximize the benefit of these drugs.

A second important question is the best biomarker to improve the selection of patients who will best respond to therapy and the testing in optimal tissue. The FDA approved alpelisib with a companion diagnostic test, the therascreen® PIK3CA RGQ PCR Kit (QIAGEN Manchester, Ltd.), to identify patients with PIK3CA mutations in tumor tissue or circulating plasma tumor DNA (ctDNA). The recommendation is that if the test is negative for PIK3CA mutations in plasma, patients should undergo testing...
for PIK3CA mutations in tumor tissue. Even with this market approval, the four articles address important issues concerning the ease of performing testing in the primary versus metastatic tissue or in ctDNA, considering the potential risks and benefits of each approach. These different and effective platforms to determine PI3K mutations aside, other novel strategies are under evaluation to better refine the population to be treated (e.g. composite biomarkers or different RNA/protein expression profiles).

Finally, the authors speculate about the best clinical strategy to further move PI3K inhibitors into the clinic, now that CDK4/6 inhibitors have clearly demonstrated a clinically relevant benefit in progression-free survival and overall survival [5–13] and are standard of care in the first and second line of treatment for luminal metastatic disease.

How the inclusion of PI3K inhibitors in the clinic might contribute to increased chemotherapy-free periods for patients remains to be seen. Sequential and concomitant strategies are being explored, and we also await overall survival data in luminal tumors with these agents. The equally relevant subject of targeting this pathway in HER2-positive or triple-negative breast cancer is also briefly discussed by Verret and colleagues and has also been extensively reviewed in other recent outstanding publications.

In summary, this compilation of PI3K-centered articles offers riveting scientific literature by summarizing the most relevant preclinical and clinical published evidence, and by helping to address the questions that still remain. Current challenges aside, I believe that this pathway wager has shown return on investment through the bench-to-bedside translation of benefits.

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