PI3K signaling pathway – a new target for breast cancer treatment

Introduction

At the 37th annual San Antonio Breast Cancer Symposium, SABCS, a number of interesting research trends, novelties as well as comprehensive summaries over studies and management of breast cancer treatment/therapies were presented. SABCS is the world’s largest breast cancer meeting, where the latest data are presented and it is therefore a gathering point for global stakeholders. This year almost 8,000 delegates from nearly 100 countries participated. This article describes a specific signaling pathway in breast cancer cells, where PI3K is one of the key molecules. This pathway may also be a target for new drugs in order to improve the management of breast cancer patients.

Background about the PI3K signaling pathway

Studies concerning PI3K and breast cancer have been ongoing for two decades. What is PI3K? It stands for phosphatidylinositol 3-kinase and it is an enzyme (kinase is a type of enzyme that catalyses transfer of phosphates), which is involved in how signals from the cell surface modulate intracellular processes. Phosphorylation, is the addition of a phosphate group to a protein or other organic molecules and this “process” (phosphorylation) turns many enzymes on and off, thereby altering their function and activity. This “phosphorylation process” plays a significant role in many cellular processes, e.g. in the PI3K pathway.

The PI3K-signalling pathway is, apart from being one of the most frequently altered pathways in cancer, regulating a number of processes within the cell. When functioning normally, the PI3K pathway regulates key cell functions such as; cell survival, proliferation, cell growth and intracellular messaging. There are different classes of PI3Ks and they differ in function and structure. The pathway is activated by growth factors binding either to receptor tyrosine kinases or G-protein coupled receptors. PI3K pathway exerts its function through its downstream molecule Akt in regulating various cell functions including cell transformation, cell proliferation, cell apoptosis, tumor growth and angiogenesis. Negative regulation of this pathway is conferred by the PTEN gene (phosphatase and tensin homolog), which acts as a tumor suppressor. PTEN regulates the cell cycle through inhibiting cell growth.

Disturbances in the PI3K-pathway result in dysregulation of many cellular functions, which can contribute to the development of cancers, e.g. breast cancer. Disturbances can be caused
by mutations in PI3K and by mutations, amplification, and loss of Akt and PTEN. Once a mutation occurs, new cells originating from the mutated cell will also carry the mutation. A
mutation cannot be corrected, but the influence of a mutated cell can be controlled and regulated by compensation mechanisms. In case of PI3K, specific inhibitors may be used. These inhibitors block signals from PI3K and/or slow down or eliminate the uncontrolled growth of mutated cells. Since the PI3K pathway plays an important role in the development and progression of malignant tumors and frequently is activated in breast cancer, great attention has been paid for the development of new agents targeting PI3K.

**Breast cancer subgroups**
experimental models, including PTEN-deficient cells, and in cells overexpressing HER2. Tumor cells that have acquired endocrine resistance have shown upregulation of HER2 levels
as well as PI3K/AKT/mTOR activation. Inhibition of the PI3K pathway has also been shown to reverse such anti-estrogen resistance.

Breast cancers of the luminal A and luminal B molecular subtypes (based on gene expression profiling) are typically ER+. Patients with luminal B tumors benefit less from adjuvant anti-estrogen therapy. This may be explained by the higher PI3K activity in luminal B breast cancer.

PI3K alterations in HER2+ breast cancer

Most patients bearing breast cancers with amplification or overexpression of HER2 benefit from anti-HER2 therapy, e.g. trastuzumab, lapatinib, pertuzumab or TDM1. Eventually, most patients with HER2+ metastatic disease though, acquire resistance to these drugs. The activation of PI3K-pathway has been suggested to be one explanation for resistance to anti-HER2 treatment. Therefore, patients with drug-resistant HER2+ breast cancer are a subgroup where focus on exploratory trials with PI3K pathway inhibitors are at hand.

To summarize - somatic mutations of PI3K identify cancers with aberrant activation of this signaling pathway and may be useful when selecting patients for trials with PI3K inhibitors.

There seem to be an agreement within researchers that initial phase II efficacy studies with PI3K inhibitors in patients with advanced disease should be focused on patients with mutations and/or activation of the PI3K pathway. As with other targeted therapies, only a small proportion of patients will probably benefit from single-agent PI3K-directed therapy.

PI3K pathway inhibitors are being tested in human trials in combination with inhibitors of HER2, MEK and ER. Early clinical data suggest that this strategy is feasible and that, as single agents, these drugs are well-tolerated.

To determine if PI3K inhibitors will prove to be a benefit compared to standard targeted therapies additional randomized clinical trials are required.

The two studies presented at SABCS 2014 In the FERGI-study, a phase II (Part 1) study, which was presented by Dr Ian Krop, assistant professor at Harvard Medical School, the hypothesis was that an active PI3K-pathway is one important reason for resistance to endocrine therapy. This hypothesis was based on earlier...
findings that 40-45 % of ER+ breast cancers harbour a PI3K mutation (PIK3CA-gene) and that PI3K/mTOR signaling had implicated resistance to anti-estrogen therapies. The FERGI-study was aiming at overcoming resistance through adding the PI3K inhibitor pictilisib to
fulvestrant. Pictilisib is a small-molecule Class 1 PI3K inhibitor available for oral intake. The study was a two-arm randomized trial of a total of 168 postmenopausal patients with ER+ and HER2- and aromatase inhibitor resistant advanced or metastatic breast cancer. They should not have had more than 1 chemotherapy treatment or 2 endocrine treatments before entering the FERGI study. One arm (arm 1) with 89 patients received fulvestrant + pictilsib and the other arm (arm 2) with 79 patients received fulvestrant + placebo. Participants in the second arm could later cross over to pictilisib + fulvestrant if/when they showed progression. In the arm randomized to fulvestrant + pictilisib the dose had to be modified and/or intake of pictilisib discontinued in some participants. Discontinuation was due to other reasons than progressive disease. Dose reduction was to some extent due to gastrointestinal reasons. The median progression free survival was prolonged from 5.1 to 6.6 months for patients in the pictilisib-containing arm. This positive effect was, however, not statistically significant (p=0.10). Exploratory subgroup analyses demonstrated potential activity in patients with ER+/PR+ breast cancers (median progression free survival 3.7 months vs 7.4 months). The effect of pictilisib was not related to PI3K mutation status. It was also concluded that the side-effects has to be taken into account as they were not negligible.

The OPPORTUNE-study was presented by Professor Peter Schmid, Centre Lead for the Centre for Experimental Cancer Medicine, London, and is a neoadjuvant study where 75 postmenopausal women with ER+ and HER2- breast cancer were randomized to either anastrozole or anastrozole + pictilisib for 14 days (+/- 2 days) before surgery. 5 patients in the pictilisib-anastrozole arm were excluded due to not fulfilling the trial criteria. This is a window-of-opportunity trial aiming at finding out whether a PI3K inhibitor – Pictilisib – can help ER positive early breast cancer patients through a preoperative treatment. Tumor tissue was available both before and after the treatment and a comparison – a biomarker analysis - could be done after the treatment. The aim of the study was to identify the patients who would benefit from this preoperative/neoadjuvant treatment. The primary endpoint was the change in tumor cell proliferation, as measured with Ki67 (immunohistochemistry). The secondary endpoint was:

- Induction of tumor cell apoptosis
- Safety and tolerability

Tertiary endpoint was treatment effect on
- Molecular subtype (PAM50 Nanostring)
- Baseline tumor cell proliferation (Ki67 IHC)
Summary: (copied as stated in the presentation)

Addition of PI3K inhibitor Pictilisib significantly increased the anti-proliferative response to Anastrozole in ER+ early BC.

Patients with Luminal B or highly proliferating tumours had an increased benefit of Pictilisib.

PIK3CA mutations or PTEN status were not predictive of response to Pictilisib.

Addition of Pictilisib to Anastrozole was not associated with an increase in tumour cell apoptosis.

The safety profile of the combination is acceptable and consistent with other trials.

Prof. Schmid said: "The first report of a preoperative window-of-opportunity study evaluating a PI3K inhibitor in early breast cancer demonstrated that addition of pictilisib to anastrozole was associated with increased anti-profilerative response over single agent anastrozole."

"However, pictilisib did not increase tumor cell apoptosis over anastrozole alone, but importantly the safety profile of the combination was "acceptable" and consistent with other trials."

In the OPPORTUNE study it was suggested that patients with early ER+ and HER- operable breast cancer could benefit from addition of pictilisib to the treatment regime. Patients with Luminal B or high proliferation tumors could also respond better to the new combination compared to ER+ tumors with low proliferation.

Overall conclusion:

Even though research of the PI3K pathway has been ongoing for a number of years, studies of PI3K-inhibitors in clinical trials are few. There are positive effects in some studies indicating that targeting this pathway may be an option for future treatment strategies. The possible positive clinical effect should, however, be considered in relation to toxicity, which seems not to be negligible.

There is also a great need to find new predictive factors for PI3K-inhibitors in order to identify those patients with the greatest benefit of the drug.
1. S2-02 The FERGI phase II study of the PI3K inhibitor pictilisib (GDC-0941) plus fulvestrant vs fulvestrant plus placebo in patients with ER+, aromatase inhibitor resistant advanced or metastatic breast cancer – Part 1 results.


2. S2-03 Preoperative window of opportunity study of the PI3K inhibitor pictilisib (GDC-0941) plus anastrozole vs anastrozole alone in patients with ER+, HER2 negative operable breast cancer (POOPRTUNE study)


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