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The prognostic value of PI3K mutational status in breast cancer: a meta-analysis

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Abstract

Breast cancer (BC) is the second most common cause of cancer-related deaths in women worldwide. The availability of reliable biomarkers of response/resistance to cancer treatments would benefit patients and clinicians allowing for a better selection of BC patients most likely to respond to a specific treatment. Phosphatidylinositol 3-kinase (PI3K) enzymes are involved in numerous cellular- functions and processes. The gene encoding for PI3K catalytic subunit p110 α is mutated in 20-40% of BC. We performed a meta-analysis of the current literature on randomized clinical trials, investigating the role of *PIK3CA* mutational status as prognostic factor and predictor of response to anti-cancer treatments. Overall 1929 cases were included. The pooled analysis confirmed that the presence of a *PIK3CA* mutation represents an independent negative prognostic factor (HR = 1.67, 95% CI: 1.15-2.43; p = 0.007) in BC, as previously reported. Since

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4. COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent for publication was obtained from all authors of this short communication.

PI3K signalling is also a result of other pathways' hyperactivation, further investigation of potential biomarkers able to predict likelihood of response to anti-PI3K/mTOR, anti-HER2 and other TKRs is warranted in future randomized clinical trials. This article is protected by copyright. All rights reserved

Keywords

Breast Cancer; Meta-analysis; *PIK3CA*; Prognostic Factor; Anti-cancer treatment response

1. Introduction

In the new era of personalised medicine, breast cancer (BC) patients are routinely offered a “molecular diagnosis” in order to allow for tailored treatments that can potentially improve their survival outcomes. These patients have benefited from major scientific and medical advances, and the fact that new targeted drugs labels now include pharmacogenomics information constitutes evidence of it. In this scenario, predictors of response to targeted therapies are needed to select the patients that are more likely to respond and monitor the therapeutic benefit in real-time.

Phosphatidylinositol 3-kinase (PI3K) proteins are a family of highly conserved enzymes involved in regulating important cellular processes, such as protein synthesis, metabolism, cell survival, proliferation, motility, intracellular trafficking, angiogenesis and apoptosis. There are three different classes of PI3K¹. The PI3K class 1 is a heterodimer composed of a regulatory and a catalytic subunit. This class is divided into Subclasses 1A and 1B on the basis of functional and structural biochemical differences². Class 1A heterodimer contains a p110 catalytic subunit isoform and a p85 regulatory subunit isoform. Class 1B has a similar structure and function, but lacks the p85-binding domain³. Under normal physiological conditions, activation of PI3K Class IA requires coupling to growth factor receptor tyrosine kinases (RTKs), including members of the human epidermal growth factor receptor (HER) family and insulin-like growth factor 1 (IGF-1) receptor⁴. On the other hand, activation of Class IB depends on the interaction with G protein-coupled receptors (GPCRs)^{5,6}.

PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP₂) to phosphatidylinositol 3,4,5- triphosphate (PIP₃). Accumulation of PIP₃ at the plasma membrane results in the recruitment of both AKT, a downstream serine/threonine kinase, and phosphoinositide-dependent kinase 1 (PDK1), an essential enzyme for the phosphorylation of AKT at Ser 308. Once phosphorylated, AKT interacts with many different effectors, including the TSC complex, constitutive inhibitor of mTORC1^{7,8}, thereby regulating RNA translation, cell growth, autophagy and protein synthesis⁹. A suppressor of this pathway is the tumour suppressor protein phosphatase and tensin homolog (PTEN), which catalyses the de-phosphorylation of PIP₃ to PIP₂. Cellular PIP₃ levels depend therefore on the competition between PI3K and PTEN^{10,11}.

The *PIK3CA* gene encodes the PI3K catalytic subunit p110 α , which is often mutated or amplified in human cancers, including BC^{12,13}. Since *PIK3CA* is mutated in 20-40% of BC^{14,15}, we performed a meta-analysis of the current literature, investigating the role of

PIK3CA mutational status as a prognostic factor and a predictor of response to anti-cancer treatments.

2. Material and Methods

The studies were identified according to the following inclusion criteria: 1) participants with BC; 2) outcome results expressed in relation to the presence of a *PIK3CA* mutation; 3) a primary outcome (disease free survival, overall survival or progression free survival) expressed as hazard ratio (HR). The following exclusion criteria were used: 1) insufficient data available to estimate outcomes; 2) animal studies; 3) size of each study arm less than 10 participants.

The summary estimates were generated using a fixed-effect model (Mantel–Haenszel method) ¹⁶ or a random-effect model (DerSimonian–Laird-method) ¹⁷ depending on the absence or presence of heterogeneity (I^2). A subgroup analysis was performed to highlight any differences between studies in terms of Overall Survival (OS), Disease Free Survival (DFS), Progression Free Survival (PFS), as summarized in table 1.

When we used the keywords “*PIK3CA mutations in early breast cancer*”, “*PIK3CA mutations in metastatic breast cancer*”, “*PIK3CA impact in breast cancer*”, the PubMed search yielded 133 potentially relevant articles; 75 studies were excluded, as duplicates. After viewing the titles and abstracts of the 58 remaining studies, the full texts of 30 studies were retrieved and 7 studies ^{13,18–23} were included in the analysis (table 1).

3. Results and discussion

A total of 1929 cases were included. BC patients were treated with adjuvant chemotherapy (such as docetaxel, cyclophosphamide, methotrexate, fluorouracil, epirubicin, vinorelbine), anti-HER2 (trastuzumab or lapatinib), endocrine therapy (such as goserelin, tamoxifen), or a combination of these treatments, including a surgical component in some cases (table 1). The pooled analysis revealed that the presence of a *PIK3CA* mutation is a negative prognostic factor (HR = 1.67, 95% CI: 1.15-2.43; $p = 0.007$, figure 1) in BC. The analysis was performed using a random-effects model due to the high heterogeneity ($I^2=70\%$).

The PI3K/AKT/mTOR pathway is one of the most commonly dysregulated pathways in patients with BC. Our meta-analysis evaluates the impact that mutations of *PIK3CA* have over prognosis of patients in different clinical settings. The most common point mutations in this gene occur at the p110 α cluster around 2 hotspots: E542/5 (exon 9) in the helical domain, and H1047 (exon 20), close to the catalytic domain. Such mutations result in amino acid substitutions (E545K, E542K, and H1047R) ¹², ultimately increasing the PI3K holoenzyme activity ²⁴ and resulting in constitutive AKT activity ^{24,25}.

Due to the complexity of this signalling pathway, targeting PI3K is challenging. While pan-PI3K inhibition is often plagued by high toxicity ²⁶, targeting only one of the multiple PI3K isoforms could eventuate in parallel activation of other signalling pathways and ultimately lead to drug resistance ^{27–30}. Both pan-PI3K (e.g. NVP-BKM-120/Buparlisib, GDC-0941/Pictilisib and BAY 806946/Copanlisib) and PI3K isoform-specific inhibitors (BYL719/

Alpelisib and GDC-0032/Taselisib) were developed. Pan-PI3K inhibitors Pictilisib and Buparlisib were discontinued due to the high toxicity, while the isoform-specific inhibitors Alpelisib and Taselisib have shown promising results in terms of anti-tumour activity (in monotherapy and in combination with anti-hormone therapies), with “expected” and more manageable side effects^{31,32}.

PI3K/AKT is the major pathway downstream of HER2. Mutations of *PIK3CA* occur in nearly 25% of HER2 overexpressing BC and are associated with poorer outcome and response to tyrosine-kinase inhibitors, such as lapatinib and trastuzumab³³. Moreover, *PIK3CA* mutations or *PTEN* loss are associated with resistance to trastuzumab, via hyperactivation of PI3K-mTOR pathway^{34–38,34} both at a preclinical and clinical level. The combination of anti-HER2 targeted therapies trastuzumab and lapatinib blocks PI3K signalling reverting trastuzumab resistance^{35,39}. A recent pooled analysis of data on neoadjuvant clinical trials showed that patients with *PIK3CA* mutations had lower rates of pCR in comparison to WT patients⁴⁰. Interestingly, further results from the EMILIA trial showed that PFS was not affected by the *PIK3CA* mutational status in patients treated with TDM-1, while patients harbouring *PIK3CA* mutations, treated with standard HER2 therapy, had shorter PFS compared to *PIK3CA* wild-type patients (4.3 vs. 6.4 months respectively)⁴¹.

More recently, Toomey et al. were the first to report that *PI3KCA/ERBB* mutations in patients receiving neoadjuvant docetaxel, carboplatin, trastuzumab and lapatinib may be more likely to experience pCR in comparison to wild type patients⁴².

In breast cancer models, the introduction of a pan-PI3K inhibitor reverted the anti-HER2 resistance³⁸. Based on this observation, clinical trials testing the dual pathway blockade are ongoing (NCT02038010; NCT02705859).

AKT inhibitors, such as MK-2206, and mTOR inhibitors, such as everolimus^{33,43} are also used in BC. Notwithstanding the promising results obtained in clinical trials using PI3K/AKT/mTOR inhibitors, pharmacological resistance has been shown to occur with this type of treatment. HER2+ *PIK3CA* mutated breast cancer cell line KPL-4 expressing *PIK3CA* mutant allele H1047R showed constitutive activation of the PI3K signalling pathway and pharmacological resistance to GDC-0941. *PIK3CA* knock-down by siRNA restored sensitivity to PI3K inhibition as for the parental cells⁴⁴. Dual blockade of mTOR 1/2 and HER2 resulted in anti-tumour activity in *in vitro* pre-clinical models of breast cancer resistant to anti-HER2 therapies⁴⁵. Garay et al. used the SK-BR3 cell line to demonstrate that only kinase domain (H1047R) mutations and not helical domain (E545K) mutations⁴⁶ confer resistance to lapatinib. Le et al. investigated molecular mechanisms of resistance to PI3K inhibitors demonstrating that expression of proviral insertion site in murine leukaemia virus (PIM) is able to bypass AKT inhibition, thus conferring resistance to selective PI3K α inhibitor BYL719/Alpelisib in BC cell lines. Concomitant PIM1 and PI3K blockade restored sensitivity to inhibition⁴⁷. It would be interesting to investigate the same pharmacological approach in future clinical trials.

This work has limitations. In particular, the retrospective nature of the study is intrinsically prone to bias. Furthermore, the patients included in the study had different treatment regimens (e.g. trastuzumab, chemotherapy or celecoxib) and different stages of disease that could both affect the analysis' results.

PI3K mutational status is currently used as a biomarker to identify patients likely to benefit from pan-PI3K⁴⁸ and PI3K- α ⁴⁹ targeted inhibition. In our analysis, we looked at breast cancer patients who underwent different types of treatment, not necessarily targeted therapies only. Our result is in agreement with the currently accepted view that the presence of *PI3KCA* mutations constitutes an independent negative prognostic factor in breast cancer patients, providing a relative indication of disease "aggressiveness".

The importance of PI3K signalling and high prevalence of mutations activating PI3K in breast cancer warrants further investigations to assess other potential biomarkers able to predict the likelihood of response to anti-PI3K/mTOR, anti-HER2 and other TKRs.

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Highlights

- Breast cancer is the second most common cause of cancer-related deaths in women.
- More accurate biomarkers of response to treatment and predictors of prognosis are needed
- Phosphatidylinositol 3-kinase gene is mutated in 20-40% of BC
- In our meta-analysis PI3K is an independent negative prognostic factor and correlates with a worse prognosis ($p = 0.007$)

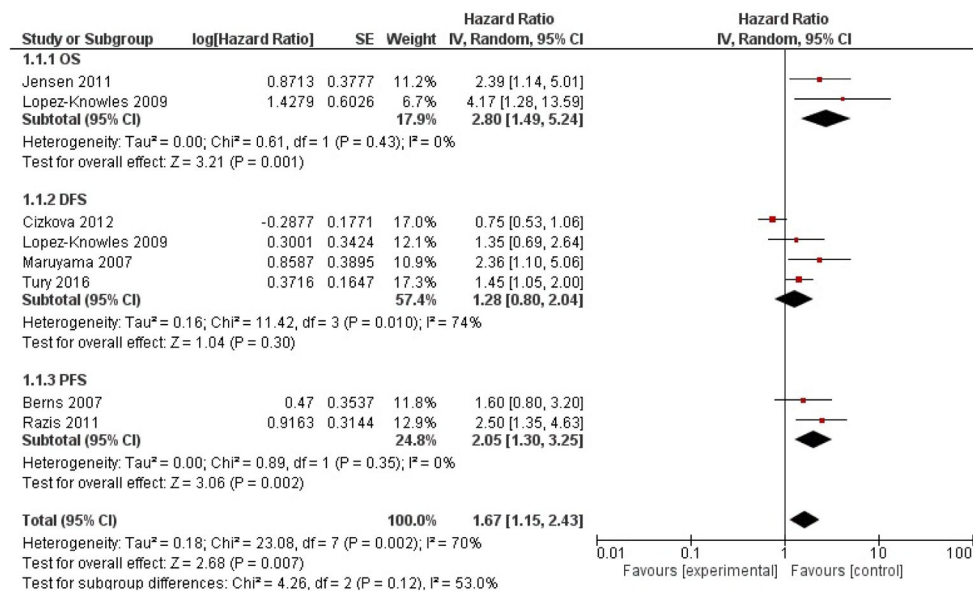


Figure 1. Forest plots of hazard ratios (HRs) according PIK3CA mutation in breast cancer.

Table 1

Characteristics of the analysed trials.

| Study | Subtype | Reference |
|--|---|---------------------------------------|
| 240 HER2+ early stage BC patients receiving adjuvant treatment were assessed before taking anti-HER2 trastuzumab therapy. | HER2+ | Jensen JD <i>et al.</i> , 2011 |
| 292 invasive BC patients treated with adjuvant therapy or chemotherapy were assessed. | Of the overall patients 68% were ER+; 57% were PR+ ; and 18% were HER2 +. | Lopez-Knowles E. <i>et al.</i> , 2009 |
| 452 unilateral invasive primary BC patients were assessed. Adjuvant therapy was given to 366 patients, which consisted of chemotherapy alone in n = 94, hormone therapy alone in n = 177, and both treatments in n = 95. None of the HER2+ patients received anti-HER2 trastuzumab therapy. | Of the overall patients 12% were HR+ (ER+ or PR+ or both) ERBB2+; 63% were HR+ (ER+ or PR+ or both) ERBB2-; 11% were HR- (ER- and PR-) ERBB2+; and 14% were HR- (ER- and PR-) ERBB2-. | Cizkova M. <i>et al.</i> , 2012 |
| 188 primary BC were assessed. One hundred patients received adjuvant hormonal therapy. Forty-seven patients received the combination of chemotherapy and hormonal therapy. Fifty-six patients developed metastases. | All subtypes | Maruyama N. <i>et al.</i> , 2007 |
| 446 BC samples collected before radio- or chemotherapy were analyzed. Three hundred sixty-one patients received adjuvant therapy, 20% consisting of chemotherapy alone, 39% consisting of hormone therapy alone, and 22% both treatments. One hundred and sixty- four patients developed distant metastases. | Of the overall patients 15% were HR-ERBB2-; 9% were HR-ERBB2+; 64% were HR+ ERBB2-; and 12% were HR+ ERBB2+. | Tury S. <i>et al.</i> , 2016 |
| 55 BC patients HER2+ with metastasis were analyzed. The following treatments were given to patients: anti-ERBB2 therapy monotherapy (5%) or anti-HER2 trastuzumab therapy plus taxane (15%), or vinorelbine (10%), or other chemotherapy (7%). | Of the overall patients 62% were HER2+. From the overall patients 25% were ER+ and 34% were ER-. | Berns K. <i>et al.</i> , 2007 |
| 256 metastatic breast cancer patients HER2+ treated with anti-HER2 trastuzumab or lapatinib treated were analyzed. | HER2+ | Razis E. <i>et al.</i> , 2011 |