Perspective

PIK3CA mutated, hormonal receptors and HER2: individual targets but partnered in the escape to targeted therapy in breast cancer

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Comment on: Loibl S, Majewski I, Guarneri V, *et al*. PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol 2016;27:1519-25.

Abstract: *PIK3CA* mutations are present in high frequency in malignant breast tumors revealing its transcendence in the biology of breast cancer. In the other hand, pathological complete response (pCR) after neoadjuvant anti-HER2 targeted therapy in estrogen receptor-positive patients is a controversial endpoint of efficacy due to the lack of correlation with long-term outcomes. In a recent paper, Loibl *et al.* report that *PIK3CA* mutations are associated to lower pCR rates, conferring resistance to neoadjuvant anti-HER2 targeted therapy in hormone receptors-positive/HER2 positive breast cancers. This and prior reports raise some questions about what is the better therapeutic strategy in HER2+/ER+ tumors bearing *PIK3CA* mutations and its prognostic value since PI3K pathway have high relevance in the escape of hormonal dependence in estrogen-positive tumors. Recent *in vitro* and *in vivo* studies suggest the benefit of targeting the PI3K pathway, HER2 and hormonal receptors in breast cancer instead HER2 as sole target.

Keywords: Breast neoplasms; neoadjuvant therapy; PIK3CA; pathological response

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Introduction

Breast cancer is the most frequent cancer in women worldwide (1). Several discoveries in the biology of this malignancy leaded to the design of anti-endocrine and targeted therapy that improved significantly the outcome of these tumors while several resistance mechanisms have been unveiled.

PIK3CA mutation is a well-known resistance mechanism with high prevalence in breast cancer. In a recent work, Loibl *et al.* [2016] described in a pool of 967 HER2+ breast cancer patients treated with neoadjuvant anti-HER2 therapy and chemotherapy that *PIK3CA* mutations were related with a significantly lower pathological complete response (pCR) rates (16.2% *vs.* 29.6%; P<0.001) (2). The subgroups analysis in this work showed statistical trends in the association with distant metastases-free survival in estrogen receptor-positive patients regardless their pathological response where *PIK3CA* mutations confers a worse outcome (P=0.0502). This study raises the question about the better strategies to manage HER2+/hormonal receptors positive breast tumors with *PIK3CA* mutations and about the benefit for these patients from targeted therapy with HER2 as the sole target.

It's well had known that PI3K pathway activation is a canonical pathway in several cancer types and a mechanism of resistance to anti endocrine therapy in ER+ breast cancer and also it provides resistance to trastuzumab treatment in HER2 tumors (3,4). Importance of *PIK3CA* in breast cancer biology has been described by several genomic projects.

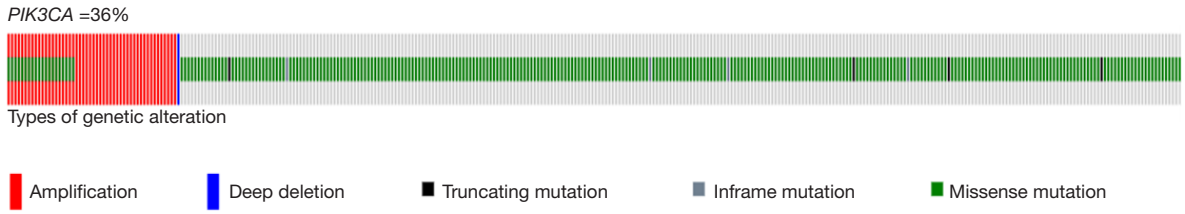

Figure 1 Frequency of *PIK3CA* mutations in TCGA data. Thirty six percent of cases harbors *PIK3CA* mutations where missense mutations are the most frequent followed by gene amplifications (TCGA data from cbioportal.org).

PIK3CA mutations in HER2 tumors confers resitance to anti-HER2 targeted therapy

Data from TCGA describe a frequency of 36% of mutations were missense mutations are the most frequent (*Figure 1*) (5). Frequency of *PIK3CA* mutations in the molecular subtypes of breast cancer is, luminal A, 45%; luminal B, 29%; HER2 enriched, 39% and basal-like, 9%. There are three hotspots *PIK3CA* mutations (≈80%) in the regions encoding the helical (E542K, E545K) or catalytic (H1047R) domains of p110α (6). Data from several populations suggests that frequency of *PIK3CA* mutations is not related to ethnicity but distribution of breast cancer subtypes (7).

PIK3CA mutations have a driver role in breast cancer (8). This gene encodes the protein p110 that participate in signal transduction of mitogenic signals, have interaction and share pathways with important drivers in breast cancer biology (*Figure 2*). *In vitro* studies have shown that a small increase in the expression of *PIK3CA* wild type is sufficient to confer resistance to trastuzumab while HER2 cell lines harboring *PIK3CA* mutations are resistant to trastuzumab alone and in combination with lapatinib or pertuzumab (4,9).

Biomarkers evaluation in the most important trials with anti-HER2 targeted therapy leaded to the association of lower response rates in patients with *PIK3CA* mutated. In the NeoALTTO trial, differences in pCR were highly significant (53.1% *vs.* 28.6%, for *PIK3CA* wild type *vs.* mutated, respectively; P=0.012) (10).

In the pooled analysis by Loibl *et al.* [2016], there were not differences in rates of pCR in the subgroup of HR– patients (36.4% *vs.* 27.2%; P=0.125, for *PIK3CA* wt *vs.* mutant, respectively); however, this difference was highly significant in HR+ patients (24.2% *vs.* 7.6%; P<0.0.001, for *PIK3CA* wt *vs.* mutant, respectively). Interestingly, when comparison was done according to treatment, there were differences in the group of patients receiving trastuzumab plus lapatinib. There was observed a slight advantage in terms of disease-free survival in patients with *PIK3CA* wild type (P=0.0502) (2).

The lack of prognostic significance of *PIK3CA* mutations in hormone receptor negative patients could be explained by the types of mutations. In the study of Pereira *et al.*, evaluating 2,433 breast cancer patients, it was observed a significant enrichment of mutations in codons 345, 542 and 545 in estrogen receptor positive tumors while in estrogen negative, mutations in codon 1047 were most frequent (11).

In the other hand, PI3K inhibition increase ER expression and tumor cells trend to adopt patterns of luminal A gene expression, for this reason is a good idea to combine anti-endocrine therapy with PI3K inhibitors in order to overcome the resistance (12).

What is the value of pCR in the outcome of HER2+/HR+ breast cancer?

pCR as surrogate of disease-free or overall survival (OS) is controversial although is frequently used as endpoint for approval in clinical trials. A meta-regression of 29 randomized neoadjuvant trials described only a weak association between odds ratios with hazard ratios for disease-free or OS (13).

It's well known that luminal tumors achieve low rates of pCR after the neoadjuvant chemotherapy and this not influence the outcome (14). In regard to HER2+ tumors treated with anti-HER2 targeted therapy, data from the NeoALTTO study showed that pCR is associated to a better event-free survival only in the group of hormone receptors negative patients (HR =0.34; 95% CI: 0.17–0.63; P=0.001) in contrast to hormone receptors positive patients where significant differences were not observed (HR =0.50; 95% CI: 0.18–1.13; P=0.13) (15). In a pooled analysis of 11,955 patients from 12 neoadjuvant trials, the subgroup analysis show no improving in OS in HER2 positive, hormone-receptor positive patients treated or not with trastuzumab (HR =0.56, 95% CI: 0.23–1.37 and HR =0.57, 95% CI: 0.31–1.04), although the analysis in all HER2+/ hormonal receptors-positive patients, the benefit for patients achieving pCR was evident (16).

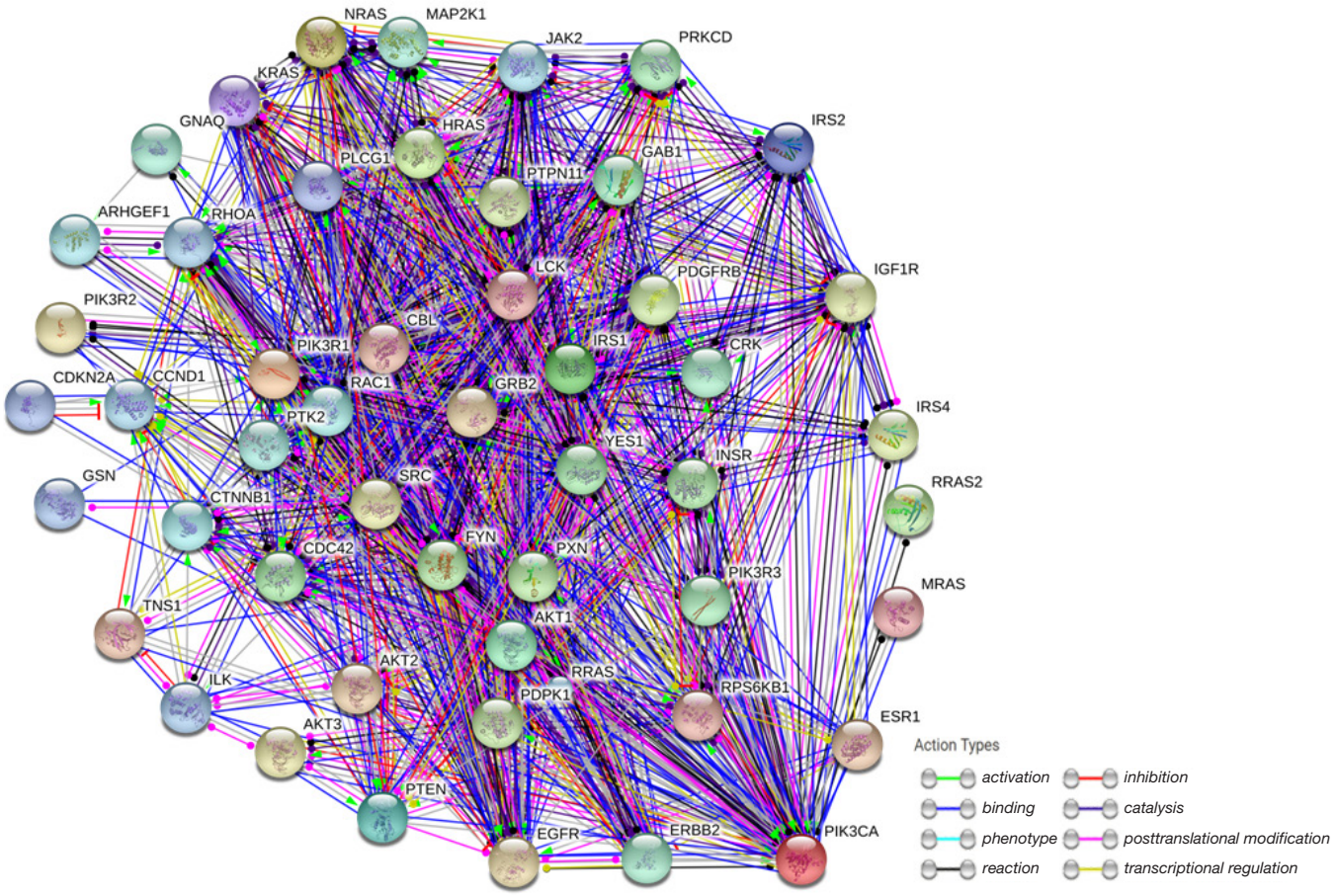

Figure 2 Interaction of PIK3CA with other gene products. Analysis in the platform String-DB reveals the intricate interaction between PIK3CA (in red) and other proteins of importance in breast cancer as encoding the estrogen receptor alpha (ESR1) and encoding the HER2 receptor (ERBB2). Interactions were predicted with a minimum required interaction score of 0.9 with no more than 50 interactions.

Future perspectives

HER2-positive breast cancer corresponds to a superfamily of breast tumors (as coined by von Minckwitz) with great molecular complexity (17). Although expression of hormone receptors in HER2 tumors is associated with better outcome, mechanisms of resistance could be developed compromising the efficacy of the targeted therapy (18). *PIK3CA* mutations are one of these mechanisms.

Several *in vitro* and *in vivo* studies have shown that use of combined therapy targeting MAPK and HER2 could be an effective treatment approach in patients HER2+/*PIK3CA* mutated whilst molecular data from clinical trials revealed the importance of to determine the mutational status of PIK3CA supported by the inclusion of PIK3CA/MTOR/AKT inhibitors in the therapeutic strategies (19).

Despite the evidence, there is questions regarding why ER-negative tumors seems more sensitive than ER-positive tumors to combination of anti-HER2 therapy and PIK3CA/MTOR/AKT inhibitors. In the BOLERO-1 trial of combination of everolimus (or placebo) with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer was observed a clinical benefit in the ER-negative group (although not statistically significant by parameters chosen by the investigators) (20). This finding was also corroborated in BOLERO-3 trial in women with trastuzumab and paclitaxel resistant breast cancer that were randomized to receive everolimus plus trastuzumab and vinorelbine or to placebo plus trastuzumab plus vinorelbine. The benefit for everolimus addition was seen in ER-negative patients. The biomarkers study in this trial showed a benefit in PTEN low and pS6 high tumors (21). In addition, *PIK3CA* mutations

was not predictive for benefit to everolimus despite this mutation produce a phenotype similar to PTEN low, indicating additional mechanisms of resistance.

In the other hand, the BOLERO-2 trial showed that addition of anti-endocrine therapy to everolimus is better than only everolimus in hormone receptors-positive patients (22).

Future studies will add a better characterization of resistance mechanisms. Currently, there are 26 clinical trials in breast cancer with PIK3CA inhibitors registered in clinicaltrials.gov while basic research find new mechanisms of resistance such as *PIM1*, recently involved in resistance to PIK3CA inhibitors (23).

Although PIK3CA, HER2 and hormonal receptors cooperate in the resistance to targeted therapy in breast cancer; data from BOLERO-2 and BOLERO-3 trials suggest that targeting PI3K pathway can reverse the resistance to HER2 and endocrine therapy in pre-treated patients. A better characterization of mechanisms of resistance should be done in order to identify patients that will benefit of targeted therapy.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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