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Clinical Implications of Mutations in the PI3K Pathway in HER2+ Breast Cancer: Prognostic or Predictive?

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Abstract

Recent advances in tumor genetics and drug development have led to the generation of a wealth of anti-cancer-targeted therapies. These drugs aim at targeting a particular vulnerability in the tumor generated in most cases as a result of dependence on an oncogene and/or loss of a tumor suppressor. Genes in the phosphoinositide 3-kinase (PI3K)/AKT pathway are the most frequently altered in human cancers. Aberrant activation of the PI3K/AKT pathway has been shown to confer resistance to HER2-targeted therapies. Several drugs targeting PI3K/ATK have been developed and are currently in clinical trials in different phases of clinical development, alone or in combination. The impact of mutations in the phosphoinositide 3-kinase (PI3K)/AKT pathway in HER2-amplified breast cancers will be the focus of this review.

Keywords

Phosphoinositide 3-kinase (PI3K)/AKT; Mammalian target of rapamycin (mTOR); Pathway inhibitors; Breast cancer; Mutation; Clinical trials; Breast cancer

Introduction

Breast cancer therapy is currently guided by clinical staging as well as analysis of biological features of the tumor, such as HER2 overexpression [1]. Despite the use of HER2-targeted agents, many patients with HER2+ tumors have intrinsic resistance (de novo, i.e., tumors that do not respond to a drug from the onset of therapy) to HER2-targeted therapies, and many patients will eventually acquire resistance (i.e., tumors that initially respond to therapy but subsequently resume growth) to these treatments after an initial response [2]. Intrinsic (de novo) resistance is evidenced by lower objective response rates (ORR) achieved with

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Compliance with Ethical Standards

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these agents upfront [3]. Acquired resistance may occur as tumor cells adapt to the stress of treatment by using alternate cellular signaling pathways [3, 4]. Inherited and acquired resistance to a given targeted agent could be explained by several different phenomena, including but not limited to compensatory cross talk with other signaling pathways, molecular changes in the target receptor, alterations in the regulation of downstream signaling components, steric inhibition imposed by other cellular elements, and pharmacogenetic alterations in the host [4, 5].

Advances in tumor genetics and drug development have led to the generation of a wealth of anti-cancer-targeted therapies. These drugs aim at targeting a particular vulnerability in the tumor generated in most cases as a result of dependence on an oncogene and/or loss of a tumor suppressor. Several recent examples indicate these drugs are mainly, if not exclusively, active against tumors of a particular genotype that can be identified by a diagnostic test, usually detecting a somatic alteration in tumor DNA. The impact of mutations in the phosphoinositide 3-kinase (PI3K)/AKT pathway in HER2-amplified breast cancers will be the focus of this review.

The Phosphoinositide 3-kinase (PI3K)/AKT Pathway

The PI3K/AKT pathway is frequently mutated in human cancers, with mutation and/or amplification of the genes encoding the PI3K catalytic subunits p110α (*PIK3CA*) and p110β (*PIK3CB*), the PI3K regulatory subunits p85α, p55α, and p50α (all encoded by *PIK3R1*) and p85β (PIK3R2), receptor tyrosine kinases (RTKs) such as HER2 (*ERBB2*), the PI3K activator K-RAS, the PI3K effectors AKT1, AKT2, AKT3, and PDK1, and loss of the lipid phosphatases PTEN and INPP4B (reviewed in [6]). The *PIK3CA*, *PIK3CB*, *PIK3CD*, and *PIK3CG* genes encode the homologous p110α, p110β, p110δ, and p110γ isozymes, respectively. Expression of p110δ and p110γ is largely restricted to immune cells and leukocytes, whereas p110α and p110β are ubiquitously expressed.

PIK3CA mutations are the most common genetic alterations of this pathway, where ≥80 % occur within the helical (E542K and E545K) and kinase (H1047R) domains of p110α. Helical domain mutations increased catalytic activity by reducing the repression of p110α by p85α [7] or facilitating the interaction of p110α with IRS-1 [8], whereas kinase domain mutations increase the retention of p110α at the plasma membrane [9]. These gain-of-function mechanisms induce cellular transformation, growth factor- and anchorage-independent growth, and resistance to anoikis. Several studies subsequently showed that tissue-specific expression of mutant *PIK3CA* can induce tumor formation and accelerate cancer progression [10–12].

PI3K/Akt Pathway in HER2+ Breast Cancer

The PI3K pathway is involved in tumor cell progression and survival in HER2+ breast cancers; HER2/HER3 dimers activate PI3K, which leads to tumor survival and growth [13]. Resistance to HER2-targeted therapies, such as trastuzumab, resulting in poor outcome and overall survival, has been associated with somatic alterations that further dysregulate the PI3K signaling pathway [14], such as *PTEN* inactivating mutations [15] or *PTEN* loss [16] and “hot-spot” *PIK3CA* mutations [17]. Pre-clinically, PI3K pathway inhibitors can

overcome trastuzumab resistance in tumors with *PIK3CA* mutation or *PTEN* loss [17, 18]. In addition, HER2+ tumors that also harbor *PIK3CA* mutations are less responsive to combinations of HER2-targeted treatments (trastuzumab/lapatinib and trastuzumab/pertuzumab) [15, 19–24].

Aberrant activation of the PI3K/AKT pathway has been shown to confer resistance to HER2-targeted therapies in various experimental models [17, 20–25]. A recent study showed that transgenic mammary tumors expressing both HER2 and PIK3CA^{H1047R} were highly resistant to the combinations of trastuzumab plus pertuzumab and trastuzumab plus lapatinib. Interestingly, the addition of the pan-PI3K inhibitor buparlisib to each combination restored drug-induced inhibition of tumor growth [26].

Clinical Trials in HER2+ Breast Cancer

Retrospective reports have shown that patients with *HER2*-amplified/*PIK3CA* mutant exhibit a lower clinical response and progression-free survival in the metastatic setting and worse disease-free and overall survival in the adjuvant setting [15, 19–22, 27, 28]. However, there is still controversy in regard to the predictive value of *PIK3CA* mutations for benefit from HER2-targeted therapies. A prospective analysis of 737 patients with HER2+ breast cancer in two large European neoadjuvant studies (GeparQuinto and GueparSixto trials) that utilized trastuzumab, lapatinib, or the combination of these drugs with chemotherapy revealed that about 20 % of tumors had a *PIK3CA* mutation. The rate of pathologic complete response in the patients with a *PIK3CA* mutant cancer vs. patients with *PIK3CA* wild-type tumors was significantly lower, particularly for patients with HER2+/ER+ breast cancer and the ones that received both lapatinib and trastuzumab [29]. Consistent with GeparQuinto and GueparSixto, analyses of the Neo-ALTTO [28, 30], Neosphere [31], and the TBCRC006 [32] phase II trials also observed that the rate of pathologic complete response seen in the patients with *PIK3CA* mutant tumors was significantly lower compared to that in patients with wild-type *PIK3CA* cancers. However, analysis of patients in a large phase III adjuvant trial which randomly assigned women with HER2-positive stage II to III breast cancer to adjuvant chemotherapy with or without 12 months of trastuzumab (NSABP B-31 trial) [33] found no difference in outcome between the *PIK3CA*-mutant (25 % of patients) and wild-type subgroups (disease-free survival hazard ratio, 0.44 vs. 0.51, respectively). A lack of statistically significant association between trastuzumab disease-free survival and overall survival benefit and *PIK3CA* mutations was also reported in the genotypic analysis of the adjuvant phase III FinHER trial [34]. More recently, a combined genotypic analysis of nearly 1000 patient from the GEPARstudies [29], Neo-ALTTO [30], and the CHERLOB [35] prospective neoadjuvant trials showed that PIK3CA mutations were associated with low pathological complete response rates, especially in patients receiving double HER2-targeted therapies; however, disease-free survival was not different between the *PIK3CA* wild-type versus mutant cohorts [36].

In the CLEOPATRA study [37], which randomized patients with HER2-positive metastatic breast cancer without prior treatment in the metastatic setting to receive taxane-based chemotherapy and trastuzumab with or without pertuzumab, 32 % of patients were found to have a *PIK3CA* mutation in their tumor. While the overall median progression-free survival

for these patients was lower, the benefit from pertuzumab addition was proportionally maintained [27], suggesting that the presence of a *PIK3CA* mutation is a relevant prognostic factor but not a predictive one.

Two phase III clinical trials explored the targeting of the PI3K axis in addition to HER2 as a potential strategy to overcome resistance in the metastatic setting. BOLERO-3, a phase III randomized trial of trastuzumab and vinorelbine with or without everolimus in women with *HER2*-amplified metastatic breast cancers refractory to prior HER2 therapies, showed a modest but statistically significant increase in progression-free survival, and patients with ER+/HER2+ tumors did not seem to benefit as much as patients with ER-/HER2+ tumors [38]. BOLERO-1 [39], a phase III randomized trial of trastuzumab and paclitaxel with or without everolimus in women with *HER2*-amplified metastatic breast cancers without prior HER2 therapy in the metastatic setting, did not show any benefit overall from the addition of everolimus, except for a non-statistically significant modest improvement in progression-free survival in patients with ER-/HER2+ breast cancers. Interestingly, in both trials, tumors with presence of a *PIK3CA* mutation (which accounted for about 30 % of patients in each trial) or low *PTEN* expression and high pS6 had higher benefit to the everolimus addition, whereas no benefit was seen in tumors without these alterations, suggesting that PI3K/AKT/mTOR pathway activation may be a marker of sensitivity to PI3K pathway inhibitors in metastatic HER2+ breast cancer.

A phase I/Ib dose escalation study of BEZ235 (Novartis), a dual PI3K/mTOR inhibitor, with trastuzumab aimed to enrich for patients with PI3K pathway alterations by limiting the study to patients with mutations in *PIK3CA* or *PTEN* or loss of PTEN by IHC in tumor samples [40]. Despite clinical activity, the combination was ultimately found to be too toxic, and the study was discontinued. Several other phase I, II, and III trials with various PI3K inhibitors are ongoing (Table 1). NeoPHOEBE (NCT01816594) is a prospective, phase II randomized trial of neoadjuvant paclitaxel and trastuzumab with or without the pan-PI3K inhibitor buparlisib (BKM120) for treatment of stage II and III HER2+ breast cancers that will try to clarify these observer discrepancies. A phase Ib trial for patients with HER2+ metastatic breast cancer, with three cohorts of different HER2-targeted therapies (trastuzumab, pertuzumab; trastuzumab, pertuzumab, paclitaxel; and TDM1), is being planned and will be exploring the addition of taselisib (GDC-0032; Genentech), a β-sparing PI3K inhibitor, to HER2-targeted treatments in both *PIK3CA* mutated or wild-type tumors.

Conclusion

In summary, *PIK3CA* mutation status may not yet be a reliable predictive biomarker for selection of HER2-targeted therapies in early stage disease. It is certainly prognostic, as patients with a *PIK3CA* mutation have lower rates of pCR. However, the presence of a *PIK3CA* mutation does not negate the beneficial effect of HER2-targeted therapies as there is no difference in long-term outcome (disease-free survival and overall survival for stage I, II, and III patients).

We recognize though that there may be differences in the interactions between *PIK3CA* mutation status and HER2 overexpression in the primary tumor vs. metastases. As in the

early setting, a *PIK3CA* mutation has prognostic implications and is associated with worse outcome for patients with metastatic disease. Nevertheless, despite maintaining benefit from HER2-targeted therapies, the presence of a *PIK3CA* mutation seems to confer benefit from PI3K/Akt/mTOR pathway inhibition (i.e., through everolimus use). Therefore, continuing efforts in exploring PI3K inhibitors/HER2-targeted combinations for patients with metastatic HER2+ breast cancer are certainly justified.

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Table 1

Ongoing clinical trials with PI3K inhibitors in HER2+ breast cancer

Trial type	Type of PI3K inhibitor	Clinical trial name	Identifier
Phase I/II	α-Specific PI3K inhibitor	BYL719+ T-DM1 in HER2(+) metastatic breast cancer pts who progress on prior trastuzumab and taxane treatment	NCT02038010
	Dual PI3K/mTOR inhibitor	A phase Ib/II study of BEZ235 and trastuzumab in patients with HER2-positive breast cancer who failed prior to trastuzumab	NCT01471847
	Pan-PI3K inhibitor	Study of XL147 (SAR245408) in combination with trastuzumab or paclitaxel and trastuzumab in subjects with metastatic breast cancer who have progressed on a previous trastuzumab-based regimen	NCT01042925
		Safety and efficacy of BKM120 and lapatinib in HER2+/PI3K-activated, trastuzumab-resistant advanced breast cancer (PIKHER2)	NCT01589861
Phase II		NeoPHOEBE: Neoadjuvant trastuzumab+BKM120 in combination with weekly paclitaxel in HER2-positive primary breast cancer	NCT01816594