Outcome impact of PIK3CA mutations in HER2-positive breast cancer patients treated with trastuzumab

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Background: Phosphatidylinositol 3-kinase (PI3K) pathway activation has been suggested to negatively influence response to anti-HER2 therapy in breast cancer patients. The present study focused on mutations of the PIK3CA gene, encoding one of the two PI3K subunits.

Methods: PIK3CA mutations were assessed by direct sequencing in 80 HER2-positive patients treated with 1 year of trastuzumab. All patients preoperatively received four cycles of anthracycline-based chemotherapy, followed by four cycles of docetaxel and 1 year of trastuzumab, starting either before surgery with the first cycle of docetaxel and continuing after surgery (neoadjuvant trastuzumab arm, n = 43), or only after surgery (adjuvant trastuzumab arm, n = 37).

Results: PIK3CA mutations were found in 17 tumours (21.3%). Better disease-free survival (DFS) was observed in patients with PIK3CA wild-type compared with mutated tumours (P = 0.0063). By combining PIK3CA status and treatment arms, four separate prognostic groups with significantly different DFS (P = 0.0013) were identified.

Conclusion: These results confirm that the outcome of HER2-positive patients treated with trastuzumab is significantly worse in patients with PIK3CA-mutated compared with wild-type tumours.

The phosphatidylinositol 3-kinase (PI3K) pathway has been identified as an important player in cancer development and progression. Upon receptor tyrosine kinase activation, the PI3K kinase phosphorylates inositol lipids to phosphatidylinositol-3,4,5-trisphosphate. PI3K is a heterodimeric enzyme composed of a p110α catalytic subunit encoded by the PIK3CA gene and a p85 regulatory subunit encoded by the PIK3R1 gene. Phosphatidylinositol-3,4,5-trisphosphate activates the serine/threonine kinase AKT, which in turn regulates several signalling pathways controlling cell survival, apoptosis, proliferation, motility, and adhesion (Zhao and Vogt, 2008; Baselga, 2011).

Recent reports suggest that the PI3K pathway activation could negatively influence response to trastuzumab therapy. This observation was described on both retrospective and prospective patient series (Dave et al, 2011; Wang et al, 2011; Jensen et al, 2012). Jensen et al (2012) described a statistically significant poorer
PIK3CA mutations were found in 17 tumours (21.3%), of which 4 were in exon 9 and 13 were in exon 20. No significant associations were found between PIK3CA mutations and classical clinicopathological characteristics (Supplementary Table S1). No significant difference in pCR was observed between PIK3CA-mutated and wild-type tumours.

Survival analysis found significantly lower DFS in PIK3CA-mutated cases in the overall population \((P = 0.0063; \text{Figure 1})\). More detailed analysis of the four-patient subgroups based on treatment arm and PIK3CA status demonstrated statistically significant differences in patient outcome \((P = 0.0013; \text{Supplementary Figure S1})\). The most favourable survival was observed in the subgroup of patients without PIK3CA mutations treated in the neoadjuvant trastuzumab arm and the poorest prognosis was observed in the subgroup of patients with PIK3CA mutations treated in the adjuvant trastuzumab arm. Overall survival curves also differed significantly in the overall population \((P = 0.035)\) and in the treatment-based subgroups \((P = 0.028)\) in favour of PIK3CA wild-type tumours (data not showed).

**RESULTS**

**DISCUSSION**

PIK3CA is the most frequently mutated oncogene in human breast cancers and shows activating mutations ranging from 10% in the triple-negative subgroup to 40% in the hormonal receptor-positive/ERBB2-negative subgroups. Moreover, PIK3CA-mutated status confers a more favourable outcome in breast cancer patients without trastuzumab treatment (Baselga, 2011). We confirm previously published results, showing PIK3CA mutations in exons 9 and 20 and hotspots in about 20% of HER2-positive breast cancers and occurring more frequently in exon 20 (Baselga, 2011; Jensen et al, 2012). In the present study focusing on 1 year of trastuzumab treatment, patients with PIK3CA-mutated tumours had a poorer outcome than PIK3CA wild-type cases (Figure 1). A favourable survival benefit was observed when neoadjuvant trastuzumab was added early to neoadjuvant chemotherapy, particularly in patients with PIK3CA wild-type tumours (Supplementary Figure S1).
These data therefore support the negative influence of PI3K pathway activation on response to trastuzumab therapy described by Jensen et al (2012). Moreover, based on a larger series, we confirm the data reported by Dave et al (2011), who studied the effects of PIK3CA mutations on response to neoadjuvant trastuzumab therapy in a small series of 32 HER2-positive breast cancer patients. It is noteworthy that these authors similarly did not find any difference in pCR associated with PIK3CA mutations. Importantly, the results described here are derived from a prospective clinical trial of neoadjuvant patients with pretreatment tumour samples available for assessment and with well-documented follow-up. Thus, the mutational status assigned to each patient showed the therapy-naïve tumour condition before initiation of study treatment. This is an important point, especially in the light of a report by Dupont Jensen et al (2011), showing discordances between PIK3CA mutations in primary breast tumours and their metastases, which might influence the results of studies based on retrospective sample collection and advanced treatment lines.

Furthermore, the negative effect of PIK3CA mutations on response to trastuzumab therapy is also supported by similar observations in breast cancer cell lines (Berns et al, 2007; Dave et al, 2011; Jensen et al, 2012). This extends and underlines the knowledge of the effect of PIK3CA mutations and PI3K pathway activation on HER2-inhibitor treatment response observed on patient breast tumour samples. In the light of published data, PI3K pathway activation also appears to predict treatment response to the HER2-targeting tyrosine kinase inhibitor lapatinib (Eichhorn et al, 2008).

Altogether, these data suggest that only PIK3CA wild-type cancers clearly benefit from neoadjuvant trastuzumab therapy added to chemotherapy. On the other hand, the subgroup of patients bearing PIK3CA mutations could further benefit from treatment targeting PI3K pathway signalling (PI3K or its downstream major effectors; Kataoka et al, 2010; Tanaka et al, 2011; Jensen et al, 2012). Such treatment may be able to overcome the activation effect of PIK3CA mutations and block the PI3K pathway signalling. Our results support the importance of PIK3CA mutational status assessment in the management of future gene-based therapies (HER2, mTOR or PI3K inhibitors used alone or in combination) for HER2-positive breast cancer.

In conclusion, these results confirm that PIK3CA mutations are a pejorative factor in HER2-positive breast cancer patients receiving trastuzumab. PIK3CA mutations should be assessed in clinical trials testing anti-HER2 therapies and, in the future, in clinical practice.

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