PTEN Deficiency as a Predictive Biomarker of Resistance to HER2-Targeted Therapy in Advanced Gastric Cancer

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Key Words
HER2 · Gastric cancer · PTEN · PIK3CA · Trastuzumab · Lapatinib

Abstract
Background: To investigate the role of the phosphoinositide 3-kinase (PI3K) pathway activation in human epidermal growth factor receptor 2 (HER2)-targeted therapy. Methods: We evaluated the predictive roles of PI3K, catalytic alpha (PIK3CA), and phosphatase and tensin homolog (PTEN) in HER2-based therapy (either trastuzumab or lapatinib). PTEN expression and PIK3CA mutation were analyzed using immunohistochemistry and pyrosequencing. Results: Forty-eight patients received trastuzumab (n = 39) or lapatinib (n = 9) combination chemotherapy. PTEN loss was found in 47.9% (n = 23), but no PIK3CA mutations were identified. Twenty-six (54.1%) patients responded to HER2-based therapy, without a significant difference between patients with PTEN loss and those without (52.2 vs. 56.0%). Among the patients with responsive disease, time to best response did not differ by PTEN status, but the duration of response was significantly shorter for patients with PTEN loss (median 4.2 vs. 6.1 months, p = 0.04). In addition, patients with PTEN loss had a significantly shorter progression-free survival time (median 4.9 vs. 7.3 months, p = 0.047). Conclusions: PTEN deficiency is an important predictive marker for early resistance to HER2 inhibitor treatment in gastric cancer patients. This finding may be useful for the development of drug combinations and identification of patients who need a modified treatment strategy.

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Introduction

Gastric cancer is a major health problem worldwide and one of the leading causes of death in Asia. Since the majority of patients are diagnosed at an inoperable stage of the disease or experience disease recurrence, chemotherapy is a common and important treatment option for gastric cancer [1]. Although cytotoxic chemotherapy is the mainstay of treatment, newer and molecularly targeted agents have recently been incorporated into the treatment regimen, and have been reported to improve survival.

Human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase receptor and is overexpressed or amplified in 10–20% of gastric cancer [2, 3]. Trastuzumab (Herceptin; Genentech, San Francisco, Calif., USA) is a humanized monoclonal antibody for the extracellular domain of HER2. Recently, the Trastuzumab for Gastric Cancer (ToGA) study has reported a clinical benefit of trastuzumab for HER2-positive gastric cancer patients [4], making it the only targeted therapy approved by the FDA for the treatment of HER2-positive gastric cancer patients. However, because the majority of patients have intrinsic or develop acquired resistance within 1 year, elucidating the molecular mechanisms for trastuzumab resistance is warranted to improve survival in HER2-positive gastric cancer patients.

Several potential mechanisms for trastuzumab resistance have been described, including altered receptor-antibody interaction, increased Akt activity through a phosphoinositide 3-kinase (PI3K)/phosphatase and tensin homolog (PTEN) pathway aberration, reduced p27kip1, and increased insulin-like growth factor 1 receptor signaling [5]. Of these, the most likely target for rational drug development is the PI3K pathway, and as a result, it has been widely studied in HER2-positive breast cancer patients. In previous studies on breast cancer, it has been reported that low PTEN levels and/or PI3K-activating PIK3CA mutations may contribute to trastuzumab resistance [6, 7]. Based on those studies, clinical trials which combine a PI3K inhibitor with trastuzumab for patients unlikely to respond to trastuzumab-based treatment are actively ongoing. However, there have yet been no studies demonstrating the predictive value of the PI3K/PTEN pathway functionality for HER2 inhibitor treatment in gastric cancer patients. Furthermore, even the incidence of PIK3CA mutation and PTEN loss has not been described in HER2-positive gastric cancer patients. Therefore, in this study, we investigate the association between PI3K/PTEN pathway abnormalities and clinical outcomes for HER2-positive patients treated with HER2 inhibiting drugs.

Methods

Patients and Tissue Samples

Patients with HER2-positive gastric cancer were enrolled in this study at Yonsei University Hospital and Pusan Busan Paik Hospital. Between 2008 and 2012, formalin-fixed paraffin-embedded tissue blocks were obtained from a total of 48 patients. All patients had been treated with HER2 inhibitor-based therapy such as trastuzumab or lapatinib, and their clinical outcomes were recorded. HER2 positivity was defined as either or both of a 3+ score on immunohistochemical (IHC) analysis or amplified HER2 gene detected by fluorescence in situ hybridization (FISH).

Evaluation of PTEN with IHC Analysis

Formalin-fixed paraffin-embedded tissue sections (4 μm) were deparaffinized with xylene and hydrated with graded alcohol. Antigen retrieval was performed with a target retrieval solution (DAKO, Carpinteria, Calif., USA) using the pressure-cooking method, and endogenous peroxidase activity was then blocked by incubation of sections in a 1:40 mixture of hydrogen peroxide and methanol. The primary PTEN antibody (DAKO) incubation was performed at room temperature for 1 h in an antibody solution diluted to 1:100. The Real™ Envision™ HRP Rabbit/Mouse (DAKO) detection system was used as the secondary antibody, and
all sections were incubated at room temperature for 30 min. PTEN expression was labeled using a 3,3′-diaminobenzidine chromogen, and counterstaining was performed by hematoxylin.

Scoring for PTEN expression was determined by the H-score (histo-score) based on the intensity of cell staining and percentage of the staining cells as described in previous studies. Intensity was scored as 0: none, 1: weak, 2: moderate, or 3: strong. The H-score was calculated as follows: \[ H\text{-score} = (\%1 + \text{cells} \times 1) + (\%2 + \text{cells} \times 2) + (\%3 + \text{cells} \times 3). \] A H-score of \( \leq 10 \) was used as the cutoff point to designate PTEN loss based on a previous study [8, 9].

**PIK3CA Mutational Analysis**

We used a pyrosequencing assay covering the mutational hotspots of interest for the sequencing of exons 9 and 20 of PIK3CA. The exon 9 PCR primers were: PIK3CA 9-F, 5′-biotin-AACAGCTCAAAGCAATTCTACACG-3′, and PIK3CA 9-R, 5′-ACCTGTGACTCCATAGAAAATCTTT-3′. The exon 20 PCR primers were: PIK3CA 20-F, 5′-biotin-CAAGAGGCTTTGGAGTATTTCA-3′, and PIK3CA 20-R, 5′-CAATCCATTTTTGTTGTCCA-3′. Each polymerase chain reaction (PCR) mix contained the forward and reverse primers (each 10 μM), 12.5 mM each of dNTP mix, 3 mM of MgCl2, 1× PCR buffer, 1 U of AmpliTaq Gold, and 100 ng of sample genomic DNA in a total volume of 25 μl. The PCR products were electrophoresed in an agarose gel to confirm successful amplification of the 81 bp (exon 9) and 74 bp (exon 20) products. The PCR products (each 10 μl) were sequenced using the PyroMark Q24 (QIAGEN) system according to the manufacturer’s instructions.

**Statistical Analysis**

The correlation between PTEN status and clinical significance was assessed using the χ² test with statistical significance defined as a p value <0.05. We evaluated the association between the response rate, progression free survival (PFS), and overall survival (OS) with the presence of the PTEN expression using Kaplan-Meier curves with log-rank test. For categorization of the continuous PTEN expression values into PTEN loss and normal status, we chose a commonly used cut point described previously in the literature.

**Results**

**PTEN and PIK3CA Status and Their Association with Patient Characteristics**

A total of 48 patients with HER2-positive gastric cancer who received anti-HER2 treatment were enrolled. Of these patients, 39 (81.3%) used trastuzumab as first-line treatment with chemotherapy consisting of 5-fluorouracil (or capecitabine) and cisplatin. The other 9 (18.7%) patients were treated with lapatinib and taxol. Patient characteristics are summarized in table 1. The median age at first diagnosis was 61 years (range 34–79). Twenty-six (54.2%) were initially diagnosed with metastatic gastric cancer. The most frequent first metastatic sites were the liver (33.3%), lymph node (31.3%), and peritoneum (20.8%).

Cytoplasmic and nuclear expression of PTEN was frequently found in gastric cancer tissues in this study. We observed PTEN loss (H-score ≤10) in 23 (47.9%) patients and PTEN-positive tumors in 25 (52.1%) cases (fig. 1a, b). Associations between patient clinicopathological characteristics and PTEN expression are shown in table 1. PTEN expression status had no significant association with any of the clinicopathological parameters such as age, sex, metastatic sites, tumor location, histology type, stage, and previous resection.

We performed PIK3CA mutation analysis for 48 patients. Two domains, the helical domain (for codon 542 and 545 mutations) and the kinase domain (for codon 1047 mutation), were analyzed. No PIK3CA mutations were found in the 48 tumors.

**Relationship between PTEN Expression and Clinical Outcome for HER2 Inhibitor Treatment**

Among the 48 evaluable patients, 26 (54.2%) responded to HER2-based therapy. A total of 12 (52.2%) of the 23 patients with PTEN loss demonstrated clinically significant antitumor responses (two complete and ten partial responses), compared with 14 (56.0%) of the 23
Table 1. PTEN status and its relationship with clinicopathologic characteristics of 48 advanced gastric cancer patients treated with HER2 inhibitor therapy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>PTEN loss</th>
<th>PTEN positive</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>48</td>
<td>23 (47.9)</td>
<td>25 (52.1)</td>
<td></td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>61 (34–79)</td>
<td>61.5 (34–73)</td>
<td>60.5 (40–76)</td>
<td>0.68</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (83.3)</td>
<td>19 (82.6)</td>
<td>21 (84.0)</td>
<td>0.89</td>
</tr>
<tr>
<td>Female</td>
<td>8 (16.7)</td>
<td>4 (17.4)</td>
<td>4 (16.0)</td>
<td></td>
</tr>
<tr>
<td>Metastatic site</td>
<td></td>
<td></td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>Liver</td>
<td>16 (33.3)</td>
<td>8 (34.8)</td>
<td>8 (32.0)</td>
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<tr>
<td>Lymph node</td>
<td>15 (31.3)</td>
<td>6 (26.1)</td>
<td>9 (36.0)</td>
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<tr>
<td>Peritoneum</td>
<td>10 (20.8)</td>
<td>5 (21.7)</td>
<td>5 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>2 (4.2)</td>
<td>2 (8.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>5 (10.4)</td>
<td>2 (8.7)</td>
<td>3 (12.0)</td>
<td></td>
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<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>Cardia</td>
<td>24 (50.0)</td>
<td>10 (43.5)</td>
<td>14 (56.0)</td>
<td></td>
</tr>
<tr>
<td>Body</td>
<td>17 (35.4)</td>
<td>10 (43.5)</td>
<td>7 (28.0)</td>
<td></td>
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<tr>
<td>Antrum</td>
<td>7 (14.6)</td>
<td>3 (13.0)</td>
<td>4 (16.0)</td>
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<tr>
<td>Histology</td>
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<td>0.14</td>
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<tr>
<td>Well</td>
<td>4 (8.3)</td>
<td>2 (8.7)</td>
<td>2 (8.0)</td>
<td></td>
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<tr>
<td>Moderate</td>
<td>31 (64.6)</td>
<td>12 (52.2)</td>
<td>19 (76.0)</td>
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<tr>
<td>Poorly differentiated</td>
<td>10 (20.8)</td>
<td>8 (34.8)</td>
<td>2 (8.0)</td>
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<tr>
<td>Others</td>
<td>3 (6.3)</td>
<td>1 (4.3)</td>
<td>2 (8.0)</td>
<td></td>
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<tr>
<td>Stage at diagnosis (AJCC 7)</td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>I</td>
<td>1 (2.1)</td>
<td>0</td>
<td>1 (4.0)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>11 (22.9)</td>
<td>2 (8.7)</td>
<td>9 (36)</td>
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<tr>
<td>III</td>
<td>10 (20.8)</td>
<td>5 (21.7)</td>
<td>5 (20.0)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>26 (54.2)</td>
<td>16 (69.6)</td>
<td>10 (40)</td>
<td></td>
</tr>
<tr>
<td>Previous resection</td>
<td></td>
<td></td>
<td></td>
<td>0.45</td>
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<tr>
<td>Yes</td>
<td>26</td>
<td>9 (39.1)</td>
<td>17 (68.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%) except where otherwise indicated. AJCC = American Joint Committee on Cancer.
PTEN-positive patients (table 2). However, the difference between these two groups in terms of clinical response was not statistically significant ($p = 0.76$). The median time to best response was 57 days, and it was not statistically significant by the PTEN status (median 53 vs. 72 days, $p = 0.52$).

With a median follow-up duration of 24 months, the median OS was 12.8 months. In terms of PTEN status, patients with PTEN loss showed a trend toward a shorter OS than PTEN-positive patients, although this was not statistically significant (fig. 2a; $p = 0.12$, median 11.1 vs. 14.6 months). Patients with PTEN loss had a significantly shorter PFS than patients whose tumors were positive for PTEN expression (fig. 2b; $p = 0.047$, 4.9 vs. 7.3 months). In addition, among the responders, the duration of response was shorter for the patients with PTEN loss (fig. 2c; $p = 0.04$, 4.2 vs. 6.1 months).

To evaluate whether PTEN status could predict response to homogenous HER2 inhibitor treatment, we performed subgroup analyses for the association of PTEN status and clinical response to trastuzumab-based treatment. Among the 39 patients using trastuzumab
as first-line therapy, those with PTEN loss alone demonstrated shorter PFS than those in the PTEN-positive groups (p = 0.047, median 4.6 vs. 7.3 months; online suppl. fig. 1; www.karger.com/doi/10.1159/000366426). Tumor response was not significantly different between the two groups (p = 0.9).

**Discussion**

This study is the first to evaluate predictive genetic markers for response to therapy in HER2-overexpressing gastric cancer patients who receive HER2 inhibitor treatment. These data suggest that PTEN loss plays a pivotal role in resistance to HER2 inhibitor therapy in gastric cancer.

Activation of the PI3K pathway is common in human cancer, and there are many studies which report an involvement of the PI3K/Akt/PTEN pathway in oncogenesis [10–12]. Deregulation of different components of the PI3K/Akt pathway, including PTEN deletion, PI3K gene amplification and/or mutation is widely observed in numerous human tumors [13, 14]. The PI3K signaling pathway regulates important cellular functions including growth, proliferation, migration and survival. PTEN is a tumor suppressor that dephosphorylates phosphatidylinositol-3,4,5-triphosphate (PIP3) and eventually inhibits the PI3K pathway [15]. While PI3K catalyzes the production of PIP3, PTEN antagonizes this PI3K function and negatively regulates Akt activities. Mutations in the gene encoding one of the PIK3CA are mostly located within hotspots in exons 9 and 20 of the PIK3CA gene and result in PI3K pathway activation [16]. Constitutive activation of this signaling pathway in tumor cells is associated with increased aggressiveness and resistance to therapeutic agents [12, 17]. Therefore, as a potential chemoresistant mechanism, the members of the PI3K pathway, such as PIK3CA and PTEN, have been identified as important targets of investigation.

HER2 is overexpressed in 10–20% of solid tumors and results in activation of downstream signaling molecules including Ras, Src, and PI3K/Akt pathways [18]. For HER2-positive breast cancer, trastuzumab, a humanized monoclonal antibody for the extracellular domain of HER2, is widely used with remarkable efficacy. About 15% of gastric cancer patients also show HER2 overexpression, and trastuzumab is the only approved targeted treatment for gastric cancer patients [4]. Despite early successes, almost half of the patients exhibit an initial resistance or eventually become resistant to trastuzumab treatment. The PI3K pathway has been widely studied in breast cancer patients in an attempt to elucidate underlying mechanisms of trastuzumab resistance; some of these results may also be applicable to the setting of gastric cancer.

Recent studies have reported that PTEN not only antagonizes tumorigenesis but also sensitizes breast cancers to targeted therapy with trastuzumab. After the trastuzumab

<table>
<thead>
<tr>
<th>PTEN status</th>
<th>PTEN loss</th>
<th>PTEN positive</th>
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<tbody>
<tr>
<td>Complete remission (CR)</td>
<td>2 (8.7)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>13 (56.5)</td>
<td>12 (52.2)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>8 (34.8)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>0</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>Total (CR+PR vs. SD+PD)</td>
<td>15 vs. 8 (65.2 vs. 34.8)</td>
<td>14 vs. 9 (60.9 vs. 39.1)</td>
</tr>
</tbody>
</table>

Values are n (%).
treatment, via Src inhibition, PTEN was localized in the membrane and phosphatase activity was increased [19]. Therefore, it has been suggested that PTEN deficiency can confer trastuzumab resistance, and a PI3K inhibitor combination may overcome trastuzumab resistance in PTEN-deficient breast cancer cells. Berns et al. [6] reported that an activated PI3K pathway as a result of a PIK3CA mutation or low PTEN expression confers trastuzumab resistance and is associated with poor survival and response to trastuzumab-based treatment. It has been demonstrated that PTEN knockdown mutations and constitutively activated PIK3CA mutations result in trastuzumab resistance in breast cancer cell lines, and this predictive value has been validated using patients’ tissue samples. Esteva et al. [7] have also documented that PTEN loss is significantly associated with shorter survival and poor response to trastuzumab-based treatment in breast cancer patients. These studies suggest that trastuzumab response depends not only on the ErbB2 pathway, but also on the pathways involving PI3K and PTEN.

Herein, we presented findings extending the understanding of the functional role of the PI3K pathway in gastric cancer.

A functional role for the PI3K pathway in gastric cancers has been widely suggested given the prevalence of abnormalities of this signaling pathway. One previous study demonstrated that the monoallelic loss of PTEN and PIK3CA amplification is associated with oncogenic activation and may contribute to the malignant progression of gastric cancer [20]. However, there have been several studies estimating the incidence of PIK3CA or PTEN loss in gastric cancer [20–22]; none of them reported the predictive value of those markers as clinical markers. In our study, we showed that PTEN loss contributes to an increased risk for progression, even with HER2 inhibitor treatment. In addition, when considering that even in patients who do respond to therapy, those with PTEN loss have a shorter duration of response, PTEN seems to be related to both earlier progression and secondary resistance. To our knowledge, this is the first study to demonstrate the potential role of the PI3K pathway as a predictive factor in gastric cancer.

Loss of PTEN is seen in about 20–25% of HER2-positive breast cancers, and PIK3CA mutations are also seen in 25% of the same tumors [16, 23]. However, previous work has suggested that only approximately 4–10% of gastric cancer patients carry PIK3CA mutations [21, 24]. In our study, none of the 48 gastric cancer samples carried a PIK3CA mutation, a somewhat lower prevalence compared with earlier studies. In terms of PTEN expression, our results are consistent with previous studies demonstrating up to 50% of PTEN loss in gastric cancer patients [25, 26], and we used the same standardized IHC staining and analytic method as was described in previous studies [8, 9]. It should also be noted that all cases analyzed in our study were HER2-positive gastric cancer patients, and no previous study focused specifically on this subset of patients. Therefore, this selection bias may have influenced the mutation prevalence in our study. The interpretation of our results in the broader context of PIK3CA mutations and PTEN loss in all gastric cancers might also be limited by the relatively small sample size, and larger studies are needed to verify this result. Despite these limitations, however, we conclude that in gastric cancer, compared with breast cancer, PIK3CA mutations are less frequent, suggesting that PTEN loss seems to be a major player in modulating treatment responsiveness to HER2 inhibitors.

Loss of PTEN function is associated with somatic changes such as mutations, deletions, and promoter hypermethylation. Previous studies developed and validated a robust IHC assay to detect the loss of PTEN protein in paraffin-embedded specimens using a commercially available antibody [27–29]. These studies showed the correlation between PTEN protein expression and PTEN genomic status. They revealed that loss of PTEN by IHC assay correlated with adverse pathologic features and poor survival outcome. Loss of only one PTEN allele is known to be associated with decreased recurrence time. Therefore, in case of haploinsufficiency, a second allele is commonly inactivated by additional mechanisms unde-
tectable by FISH analysis. Previous studies reported that about 30% of PTEN protein loss cases were not detected by FISH analysis [30, 31]. For this case, the evaluation of PTEN by FISH is troublesome and it may underestimate the PTEN loss. Therefore, as an alternative method, recent studies have reported that IHC is a robust and reliable assay to detect PTEN loss. IHC assay for PTEN is a useful predictive marker for PI3K inhibitors, and based on this background, clinical trials for the enriched population are actively ongoing.

Our study highlights the importance of PTEN for modulating resistance to HER2 inhibitor treatment in gastric cancer patients. Therapeutic strategies to address existing trastuzumab or lapatinib unresponsiveness or to prevent the emergence of resistance are strongly warranted. Based on previous results, trials of a PI3K inhibitor combination for trastuzumab-resistant breast cancer patients are ongoing (clinicaltrial.gov; NCT01589861 and NCT01471847). With this background, our results strongly support moving in similar directions for gastric cancer patients. In our study, the median time to best response was only 2 months, and PFS was also much shorter than in patients with breast cancer. Therefore, we hope that these results will stimulate the development of clinical trials and allow appropriate patient selection for active management of HER2 inhibitor resistance. In addition, in patients who are initially responsive but have poor prognostic markers such as PTEN loss, aggressive early combination treatment might be a successful strategy to improve survival outcome.

Due to previous success in the treatment of breast cancer, lapatinib and paclitaxel have been investigated as a second-line therapy for HER2-positive gastric cancer [32]. However, despite a 2.1-month improvement in survival, the difference between paclitaxel and lapatinib combination arms did not reach statistical significance (hazard ratio 0.84, p = 0.2088). In addition, in the recently reported phase III trial for first-line treatment [33], no survival benefit has been observed from the addition of lapatinib to capecitabine and oxaliplatin combination for HER2-amplified gastric cancer patients. Therefore, targeting of molecular mechanisms other than the epidermal growth factor signal pathway is warranted in HER2-positive gastric cancer treatment. As shown in breast cancer, the PI3K/PTEN/Akt pathway may be a promising therapeutic target for gastric cancer.

Here, we reported the importance of PTEN loss in patients at risk for progression of disease after HER2 inhibitor treatment, which may help to explain resistance to chemotherapy. Taken together with previous studies of the mechanisms of resistance, our results suggest the importance of an alternative combination strategy to prevent drug resistance. Identification of a predictive marker would stimulate the development of combination drug therapies and the careful selection of appropriate patients for these combination regimens. To validate the predictive value of this biomarker, further mechanistic studies as well as prospective trials are needed in HER2 inhibitor refractory gastric cancer.

Disclosure Statement

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References


