Wien Med Wochenschr (2010) 160/19–20: 506–512
DOI 10.1007/s10354-010-0838-6

Printed in Austria

wmw
Wiener Medizinische Wochenschrift

Resistance to HER2-targeted therapy: mechanisms of trastuzumab resistance and possible strategies to overcome unresponsiveness to treatment

Michael Hubalek, Christine Brunner, Karin Matthä and **Christian Marth**

Department of Gynecology and Obstetrics, Medical University of Innsbruck, Innsbruck, Austria

Received September 20, 2010, accepted October 6, 2010, published online October 26, 2010

Resistenz gegen HER2-gerichtete Therapie: Mechanismen der Trastuzumab-Resistenz und mögliche Strategien zur Überwindung des Nichtansprechens auf die Behandlung

Zusammenfassung. Trastuzumab ist eine hocheffektive Waffe in der Behandlung des HER2-positiven Mammakarzinoms. Dieser monoklonale Antikörper ist sowohl in der metastasierten als auch adjuvanten Situation zur Behandlung zugelassen. Trotzdem bleiben viele Fragen über den optimalen Einsatz weitgehend offen. Insbesondere die Tatsache, dass ein signifikanter Anteil HER-2 positiver Mammakarzinome primär nicht auf eine Trastuzumab-Therapie ansprechen oder nach etwa einem Jahr eine Resistenz gegenüber diesem Antikörper entwickeln, bedarf intensiver Forschungsarbeit. In dieser Zusammenfassung des aktuellen Wissenstands über die Resistenzmechanismen gegenüber Trastuzumab werden als mögliche Ursachen der extrazelluläre trunkierte HER2-Rezeptor, der Verlust des Tumor-Suppressors PTEN, die Aktivierung alternativer Signalwege (z. B. IGFR etc.) und der Verlust der Rezeptor-Antikörper-Interaktion diskutiert. Die Entwicklung von Strategien zur Aufhebung der Resistenzentwicklung stellt ein wichtiges Betätigungsfeld bei der Behandlung des HER2-neu positiven Mammakarzinoms dar.

Schlüsselwörter: HER2, Brustkrebs, Trastuzumab, Resistenzentwicklung, PTEN, PI3K, IGFR, Lapatinib, Gefitinib, Pertuzumab

Summary. Trastuzumab has shown significant efficacy in HER2-overexpressing breast cancers and is approved for patients whose tumors carry this abnormality, both in the metastatic and in the adjuvant settings. However, several issues about its optimal use remain unresolved. Many breast cancer patients with HER2 overexpression do not respond to initial therapy with trastuzumab (Herceptin®), and a vast majority of these develop resistance to this monoclonal antibody within one year. This review discusses the molecular mechanisms leading to the development of trastuzumab resistance, including circulating HER2 extracellular domain, loss of PTEN, activation of alternative pathways (e.g. IGFR), and receptor-antibody interaction block. Additionally, the possibility of exploring these aberrations as therapeutic targets that potentially overcome resistance to trastuzumab is highlighted.

Key words: HER2-positive breast cancer, trastuzumab resistance, strategies to overcome resistance, lapatinib, gefitinib, pertuzumab, PTEN, P13K, IGFR

Correspondence: *Michael Hubalek, M.D.*, Department of Gynecology and Obstetrics, Medical University of Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria.
Fax: ++43-512-504 24055, E-mail: michael.hubalek@i-med.ac.at

Introduction

The human epidermal growth factor receptor 2 (ErbB-2, HER2) is a transmembrane receptor with tyrosine kinase activity overexpressed in about 15–20% of invasive breast cancers. HER2-positive breast cancer patients have different responses to anticancer agents and a worse prognosis, thus providing shorter progression-free and overall survival than do patients with HER2-negative tumors. Trastuzumab (Herceptin®) is a humanized IgG1 monoclonal antibody against the extracellular domain of HER2 [1]. The combined use of trastuzumab and chemotherapy in randomized trials has resulted in increased overall survival in the metastatic setting and a reduced risk of recurrence and death in early-stage breast cancer.

Although trastuzumab treatment significantly improves outcome in women with ErbB2-positive breast cancers, even many patients who achieve initial response to trastuzumab acquire resistance to this antibody. Elucidating the molecular mechanisms underlying primary or acquired, i.e. treatment-induced,

resistance to trastuzumab is critical to improving the survival of patients with HER2-overexpressing tumors. Because of the complex and redundant signaling pathways of the ErbB family of receptors, which include more than 30 different extracellular domains and more than 50 intracellular effectors, there are multiple potential mechanisms involved in trastuzumab resistance. To date, there are no clinically validated markers of resistance to HER2-targeted therapy although several potential mechanisms have been proposed.

Mechanisms of action of trastuzumab

Despite the absence of a known direct ligand, the catalytic activity of HER2 is a result of its homo- and heterodimerization with other receptors of the ErbB family, such as the epidermal growth factor receptors (EGFRs) HER3 and HER4 [2]. By means of its high-affinity binding to HER2, trastuzumab is able to block intracellular signaling via the mitogen-activated protein kinase (MAPK) and the phosphatidylinositol 3-kinase (PI3K) pathways. The MAPK pathway is critical for tumor cell proliferation, and the PI3K pathway leads to phosphorylation and activation of AKT, with inhibition of apoptosis. Blocking these pathways results in accumulation of p27Kip1, an inhibitor of cyclin-dependent kinases, thus inhibiting the cyclin E/Cdk2 complex and causing cell cycle arrest in G1/S as well as induction of apoptosis.

Trastuzumab therapy also increases membrane localization and activity of PTEN, the protein product of the phosphatase and tensin homolog deleted on the chromosome 10 gene, by reducing PTEN tyrosine phosphorylation via Src tyrosine kinase inhibition. Increased PTEN activity thus inhibits the PI3K pathway and cell proliferation (Fig. 1).

Immune response activation through antibody-dependent cellular cytotoxicity is another potential mechanism of trastuzumab action [3]. Natural killer (NK) cells that express the Fc-gamma receptor are able to bind to trastuzumab and induce cell lysis. Trastuzumab was able to inhibit the outgrowth of macroscopically detectable xenograft tumors for up to seven weeks in mice inoculated with positive and intrinsically trastuzumab-resistant HER2 cells. This effect is likely to be mediated via antibody-dependent cellular cytotoxicity since the same phenomenon did not occur when trastuzumab-F(ab′) was used [4]. When overexpressed, the HER2 receptor is subject to proteolysis with subsequent cleavage and release to the circulation of the extracellular portion (p95HER2) (Fig. 2). Trastuzumab treatment inhibits the proteolytic cleavage of HER2 and prevents the production of the active truncated HER2

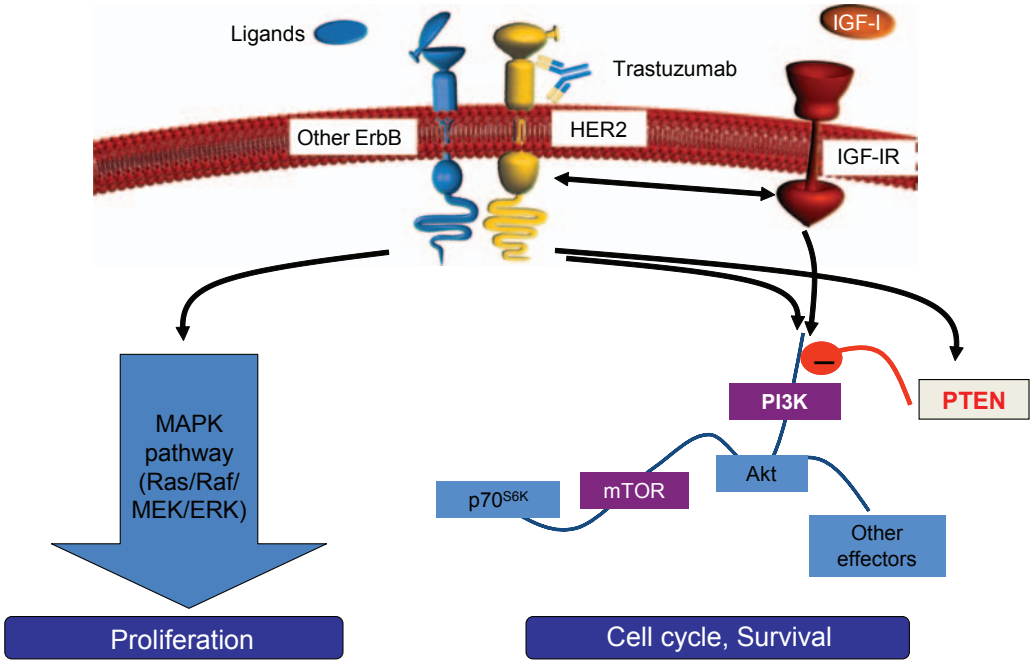

Fig. 1: Simplified illustration of key pathways involved in downstream signaling after HER2 activation. HER2 forms homodimers or heterodimers with the other members of the family. Heterodimerization is induced by the ligands of the other members of the epidermal growth factor receptor (EGFR) family. The phosphatidylinositol 3-kinase (PI3K) signaling pathway begins with PI3K activation. Phosphorylated AKT, which inhibits the activities of the transcription factors (which are mediators of apoptosis and cell cycle arrest), induces cell survival. The tumor suppressor phosphatase with tensin homolog (PTEN) negatively regulates PI3K signaling. The insulin-like growth factor–I receptor (IGF-IR) is involved in the signal cascade of the HER2 pathway and is thus also a potential target in trastuzumab-resistant breast cancer

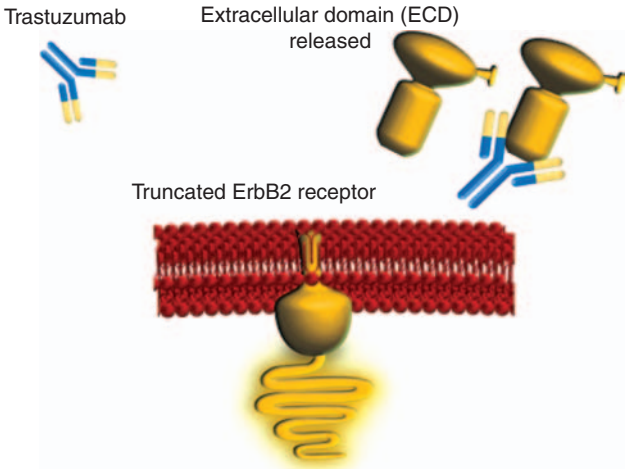

Fig. 2: The full-length 185 kDa HER2 is cleaved by matrix metalloproteases into a 110 kDa extracellular domain (ECD) that circulates in serum and a 95 kDa amino-terminally truncated membrane-associated fragment with increased kinase activity. ECD eventually binds trastuzumab and thereby competes with the activated transmembrane HER2 receptor for the opportunity to interact with the antibody

fragment, which may constitute another mechanism of action of trastuzumab [1].

Postulated mechanisms of resistance to trastuzumab (Tab. 1)

1. Extracellular receptor cleavage (receptor shedding)
HER2 may undergo proteolytic cleavage that results in the release of the extracellular domain and the production of a truncated membrane-bound fragment, p95. Trastuzumab resistance is mediated in part by the selection of p95ErbB2-expressing breast cancer cells capable of exerting potent growth and prosurvival signals through p95ErbB2 heterodimers. On the other hand, it is supposed that the inhibition of HER2 cleavage and the prevention of production of an active truncated HER2 fragment are alternative mechanisms of action of trastuzumab [1].

A high number of circulating extracellular domains can bind and inactivate trastuzumab. In a pooled analysis of 307 patients with metastatic breast cancer, individuals who did not achieve a significant decline (≥20%) in serum HER2/neu levels were seen to benefit less from trastuzumab-based therapy with or without chemotherapy. A reduction of 20% or more in the serum concentration of the HER2 extracellular domain was associated with increased progression-free and overall survival as compared with patients in whom a less strong reduction was observed (Serum HER2/neu and relative resistance to trastuzumab-based therapy in patients with metastatic breast cancer) [5]. In addition, based on an in vitro study using HER2-overexpressing breast tumor cells, Zabrecky et al., suggested that an extracellular domain can link to antibodies (e.g. Trastuzumab) against HER2, thereby competing with the activated transmembrane HER2 receptor for the opportunity to interact with the antibody [6]. This suggests another possible mechanism of resistance to treatment based on monoclonal antibodies against HER2 (Fig. 2).

2. Fc receptor status and antibody-dependent cellular cytotoxicity response
Antibody-dependent cellular cytotoxicity (ADCC) is considered to be a major aspect of the mechanism of action of trastuzumab [7]. Interactions with the Fc receptor may be a critical step in the activation of natural killer lymphocytes and ADCC response. Preliminary studies have linked both germline polymorphisms and post-

Tab. 1: Summary of proposed mechanisms of trastuzumab resistance

Supposed mechanisms of trastuzumab resistance	
Mechanism	**Example**
Obstacles preventing trastuzumab binding to HER2	MUC4 expression induces steric hindrance of trastuzumab binding to p185neu (HER2) receptor
Upregulation of HER2 downstream signaling pathways	Loss of PTEN expression and activation of PI3 K pathway creates resistance to drugs targeting HER2 tyrosine kinase signaling
Signaling via alternate pathways	Activation of IGF signaling pathway overcomes inhibition of HER2 signaling pathway
Failure to trigger an immune-mediated mechanism	Polymorphisms and other dysfunctions of Fcγ receptor reduce the antibody-derived cellular cytotoxicity (ADCC) response to trastuzumab
Extracellular receptor cleavage	p95HER2 expression enables constitutive signaling of HER2 tyrosine kinase, even when p185HER2 receptor's extracellular domain is bound by trastuzumab
Fc receptor status and ADCC response	Polymorphisms and other dysfunctions of the Fc receptor would reduce the ADCC response to infused trastuzumab

translational modifications (glycosylation and fucosylation) of the Fcγ receptor with the impaired ADCC response associated with monoclonal antibody therapeutics such as trastuzumab. The clinical development of Fc receptor assays to predict trastuzumab resistance will require their validation in prospective trials.

3. Expression of ligands of the EFGR family

Of the four members of the EGFR family, trastuzumab is the only one with no known natural ligand. Heterodimerization of HER2 with the other receptors, however, can be induced by ligands of HER1, HER3 or HER4. In the presence of an excess of ligands, HER2 or both the resulting heterodimers drive cells towards proliferation and inhibition of apoptosis [3] and, possibly, interfere with trastuzumab. Although HER2 does not have a known direct ligand, heterodimerization of HER2 with other receptors can be induced by ligands of EGFR, HER3 or HER4. In the presence of an excess of ligands, HER2 or both the resulting heterodimers drive the activation of intracellular signaling using MAPK and PI3K pathways (Fig. 2). It has been suggested that ligand overload can promote cell proliferation and diminish the effectiveness of trastuzumab. Transforming growth factor (TGF)-alpha might play an important role in this resistance mechanism. The analysis of tumor samples from three breast cancer patients performed before treatment with trastuzumab and after disease progression while still on antibody therapy demonstrated the presence of TGF-alpha only after therapy failure [8]. Moreover, in vitro expression of exogenous TGF-alpha in breast cancer cell lines was associated with a dramatic reduction in trastuzumab-induced HER2 endocytosis and cell growth inhibition. Also, HER2 gene mutations can potentially alter the interaction between the receptor and trastuzumab. Although no available studies prove such a hypothesis, the presence of somatic mutations in the region that codes for the tyrosine kinase domain has already been described in some patients.

4. Loss of PTEN

PTEN (phosphatase and tensin homolog) is one of the most commonly lost tumor suppressors in human cancer. Inactivating mutations or deletions of the PTEN gene that result in hyperactivation of the PI3K/Akt signaling pathway are increasingly reported in human malignancies, including up to 30% of breast cancers. They have been related to poor prognosis and resistance to chemo- and endocrine therapy. Patients with PTEN-deficient breast cancer have significantly poorer responses to trastuzumab-based therapy than do those with normal PTEN (Fig. 1). It has been demonstrated that the reduction of PTEN in breast cancer cell lines by means of antisense oligonucleotides conferred trastuzumab resistance *in vitro* and *in vivo* [9].

Treatment of these tumor cells with inhibitors of the PI3K pathway was capable of overcoming trastuzumab resistance. Analysis of 47 patients with metastatic breast cancer treated with trastuzumab and a taxane showed loss of PTEN expression to be associated with a weaker response [9]. Fujita et al., found a remarkable activity of trastuzumab in patients whose tumors showed elevated PTEN expression on immunohistochemistry [10]. These results suggest that loss of PTEN can be used as a predictor of resistance to trastuzumab and that the use of drugs that inhibit PI3K can provide a therapeutic alternative in patients with low PTEN concentration.

5. Activation of alternative pathways

The insulin-like growth factor-I receptor (IGF-IR) is a transmembrane tyrosine kinase receptor associated with cell proliferation and metastasis formation. The IGF signaling pathway seems to be deeply involved in breast cancer, as its ligands and receptors are frequently overexpressed, induce cell proliferation and promote metastasis. In breast cancer cell lines that overexpress HER2, an increased level of IGF-IR activation appears to interfere with the effectiveness of trastuzumab. Thus, strategies targeting the IGF-IR signaling pathway may prevent or delay development of trastuzumab resistance [11]. Cross-talk between HER2 and IGF-IR in trastuzumab-resistant, but not in trastuzumab-sensitive, cell lines has also been observed (Fig. 1). Cross-talk between IGF-IR and HER2 in resistant cells is evidenced by the fact that IGF-I stimulation results in increased phosphorylation of HER2 in such cells; conversely, inhibition of IGF-IR tyrosine kinase activity causes a decrease in HER2 phosphorylation in such resistant cells [12]. The cyclin-dependent kinase inhibitor p27Kip1 was found to be decreased in trastuzumab-resistant breast tumor cells, and cyclin-dependent kinase 2 activity increased. Importantly, the exogenous addition of p27Kip1 increased trastuzumab sensitivity. Thus, trastuzumab resistance may be associated with decreased p27Kip1 levels and may be susceptible to treatments that induce p27Kip1 expression [18]. These data suggest that reduction of p27Kip1 activity is associated with resistance to trastuzumab, possibly mediated by the heterodimerization of IGF-IR and HER2. Therefore, IGF-IR can be regarded as an important potential therapeutic target in breast cancers resistant to trastuzumab.

6. Receptor-antibody interaction blockade

Another potential mechanism related to resistance to antibody-based therapy is the development of alterations that ultimately interfere with interaction between the therapeutic agent and its target. The expression of MUC4, a membrane-associated mucin, seems to contribute to trastuzumab resistance by masking the HER2 receptor epitope. Overexpression of MUC4 has been shown to block cell–cell and cell–matrix interactions, protect tumor cells from immune surveillance, and promote metastasis. The expression of MUC4 was found to be greater in trastuzumab-resistant cell lines than in sensitive ones, and its level was inversely correlated with the trastuzumab-binding capacity of single cells. Abrogation of MUC4 expression by RNA interference increased the binding of trastuzumab. In MCF7 cell lines, the induction of MUC4 hyperexpression repressed the interaction of HER2 and HER2 antibodies, including trastuzumab. In addition, MUC4 is proposed as a ligand for HER2, and it also seems to increase the phosphorylation of HER2 and alter the signals generated by this receptor, without interfering in HER2 expression [13].

Possible strategies for overcoming resistance

Lapatinib

Lapatinib is a small molecule dual reversible inhibitor of the tyrosine kinase activity of EGFR and HER2. Preclinical studies have shown its efficacy in both HER2-overexpressing and normally expressing breast cancers by efficiently blocking signal transduction downstream from EGFR and HER2 [14]. Similar to trastuzumab, the benefit of lapatinib in breast cancer is limited to HER2-positive disease, and increased expression and activation status of HER2 are associated with response. PTEN deficiency and insulin-like growth factor-I receptor (IGF-IR) expression have been associated with trastuzumab resistance, but do not appear to preclude response to lapatinib. As previously described, p95HER2 is an altered form of the HER2 receptor resulting from the cleavage of HER2. Following cleavage p95HER2 maintains its tyrosine kinase activity although it lacks the extracellular domain of the receptor, and trastuzumab consequently no longer binds to the receptor. *In vitro*, lapatinib inhibits phosphorylation of p95HER2 and AKT with subsequent inhibition of cell growth [15]. The combination of lapatinib and trastuzumab was found to markedly enhance tumor cell apoptosis in HER2-overexpressing breast cancer cells. Currently, various clinical trials in the metastatic and adjuvant setting are evaluating the efficacy of the combination of both compounds alone and with chemotherapy. First results of a complete HER2 blockage are very promising.

Gefitinib

Treatment of breast cancer cells with a combination of the EGFR-tyrosine kinase inhibitor (EGFR-TKI) gefitinib and the anti-ErbB-2 monoclonal antibody trastuzumab results in a synergistic antitumor effect [16]. Preclinical models have shown a synergy between trastuzumab and gefitinib producing complete remissions in HER2-overexpressing breast cancer xenografts [17]. Based on this rationale, Arteaga et al., conducted a phase II study in which women with HER2-positive advanced breast cancer previously untreated with trastuzumab received a combination of weekly trastuzumab and gefitinib at a dose of 250 mg/day [18]. The study was closed at its first interim analysis because of low levels of activity, which indicated, by indirect comparison with trials using trastuzumab alone, that this combination might be antagonistic. Enrollment of patients regardless of EGFR status and suboptimal gefitinib dosing are two potential caveats of this study, which seems to contradict preclinical observations. More recently, it was shown that expression of epidermal growth factor receptor (EGFR) and HER3 was substantially increased after long-term trastuzumab exposure of HER2-positive breast cancer cell lines that express primary resistance to trastuzumab. Long-term trastuzumab exposure of trastuzumab-resistant cell lines induced *de novo* sensitivity to the EGFR-targeted agents gefitinib and cetuximab in two of three cell lines and was accompanied by increased EGFR expression [19]. Thus, EGFR inhibitors might be useful in overcoming trastuzumab-acquired resistance.

Pertuzumab

Pertuzumab is a monoclonal antibody directed against a portion of the extracellular domain of HER2 that sterically blocks the ability of HER2 to heterodimerize with other members of the family. This event impairs HER2/HER3 signaling and HER2/EGFR heterodimers in both HER2-overexpressing and non-overexpressing cells [55]. Recent work suggests that the extracellular portion of HER2 bound to trastuzumab is different from that recognized by pertuzumab. As a single agent, pertuzumab shows activity against HER2-positive breast cancer. However, in combination with trastuzumab, its level of efficacy is greatly enhanced, with an overall clinical benefit rate of 50% in 66

patients who were treated in two cohorts in a phase II study [20].

Neratinib

Similar to lapatinib, this agent is an orally available pan-ErbB TKI, differing in that it inhibits HER4 as well as HER1/EGFR and HER2. Neratinib acts in a non-reversible manner [21]. Neratinib has been tested in combination with weekly trastuzumab in a phase I/II study. The primary endpoint of the phase II study component was to achieve an increase in the 16-week progression-free survival rate from 15 to 35% with the combination. The study met this endpoint with a 16-week progression-free survival of 45% and an overall response rate of 29% [22].

Association with agents targeting other pathways

Studies of combinations of trastuzumab with inhibitors of downstream signaling are currently underway after promising results in a preclinical setting. Of these compounds inhibitors of mTOR (kinase located downstream from the PI3K-AKT pathway) seem to be of particular interest. *In vivo* assessment of biopsy samples from patients whose tumors continued to progress after trastuzumab therapy demonstrated activation of the PI3K/Akt pathway as a common mechanism underlying trastuzumab resistance [23]. Mammalian target of rapamycin (mTOR) is a serine-threonine kinase that is a downstream component of the PI3K/Akt pathway. Phase II studies are awaited. Inhibitors of PI3K are also being evaluated as potential modulators of trastuzumab sensitivity.

Modified anti-HER2 antibodies

To increase the potency of antibody-directed therapy, the specificity of the antigen-binding site has been combined with a variety of effector agents, including toxins. The first such antibody drug conjugate (ADC) in breast cancer is T-DM1, a drug linking the antimicrotubule agent maytansine to trastuzumab. T-DM1 was evaluated in a single-arm phase II study in 112 patients with previously treated HER2-positive metastatic breast cancer [24]. This study demonstrated an overall response rate of 26.9%. The response was similar among patients pretreated with both trastuzumab and lapatinib (24%).

Additionally, recombinant molecules in which the antibody-combining site is fused directly to the toxin have been developed and show a strong selectivity for HER2-binding. Antibody-bound toxins are promising, because they can be safely delivered to experiment animals at effective doses and may penetrate tumors more effectively than does trastuzumab alone.

Discussion

Improved understanding of mechanisms of resistance to trastuzumab has facilitated the development of novel agents for the treatment of HER2-positive breast cancer. Emerging data from trials conducted with these agents indicate that the HER2 pathway remains a valid therapeutic target following progression while on trastuzumab and suggest a promising role for a combined HER2 blockade employing two or more agents. In future it is anticipated that some of these agents will enter routine clinical practice in advanced HER2-positive breast cancer and may supplement or even replace trastuzumab as the backbone of adjuvant therapy. Understanding the underlying mechanisms of action of trastuzumab is critical in order to develop strategies to prevent or overcome resistance.

Conflict of interest

The authors declare that there is no conflict of interest.

References

[1] Molina MA, Codony-Servat J, Albanell J, et al. Trastuzumab (herceptin), a humanized anti-Her2 receptor monoclonal antibody, inhibits basal and activated Her2 ectodomain cleavage in breast cancer cells. Cancer Res, 61: 4744–4749, 2001.

[2] Yarden Y. Biology of HER2 and its importance in breast cancer. Oncology, 61(Suppl. 2): 1–13, 2001.

[3] Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol, 2: 127–137, 2001.

[4] Barok M, Isola J, Pályi-Krekk Z, et al. Trastuzumab causes antibody-dependent cellular cytotoxicity-mediated growth inhibition of submacroscopic JIMT-1 breast cancer xenografts despite intrinsic drug resistance. Mol Cancer Ther, 6: 2065–2072, 2007.

[5] Ali SM, Carney WP, Esteva FJ, et al. Serum HER-2/neu and relative resistance to trastuzumab-based therapy in patients with metastatic breast cancer. Cancer, 113: 1294–1301, 2008.

[6] Zabrecky JR, Lam T, McKenzie SJ, et al. The extracellular domain of p185/neu is released from the surface of human breast carcinoma cells, SK-BR-3. J Biol Chem, 266: 1716–1720, 1991.

[7] Musolino A, Naldi N, Bortesi B, et al. Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER-2/neu-positive metastatic breast cancer. J Clin Oncol, 26: 1789–1796, 2008.

[8] Valabrega G, Montemurro F, Sarotto I, et al. TGFalpha expression impairs Trastuzumab-induced HER2 downregulation. Oncogene, 24: 3002–3010, 2005.

[9] Nagata Y, Lan KH, Zhou X, et al. PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. Cancer Cell, 6: 117–127, 2004.

[10] Fujita T, Doihara H, Kawasaki K, et al. PTEN activity could be a predictive marker of trastuzumab efficacy in the treatment of ErbB2-overexpressing breast cancer. Br J Cancer, 94: 247–252, 2006.

[11] Lu Y, Zi X, Zhao Y, et al. Insulin-like growth factor-I receptor signaling and resistance to trastuzumab (Herceptin). J Natl Cancer Inst, 93: 1852–1857, 2001.
[12] Nahta R, Yuan LX, Zhang B, et al. Insulin-like growth factor-I receptor/human epidermal growth factor receptor 2 heterodimerization contributes to trastuzumab resistance of breast cancer cells. Cancer Res, 65: 11118–11128, 2005.
[13] Nagy P, Friedländer E, Tanner M, et al. Decreased accessibility and lack of activation of ErbB2 in JIMT-1, a herceptin-resistant, MUC4-expressing breast cancer cell line. Cancer Res, 65: 473–482, 2005.
[14] Nanda, R. Targeting the human epidermal growth factor receptor 2 (HER2) in the treatment of breast cancer: recent advances and future directions. Rev Recent Clin Trials, 2: 111–116, 2007.
[15] Scaltriti M, Rojo F, Ocaña A, et al. Expression of p95HER2, a truncated form of the HER2 receptor, and response to anti-HER2 therapies in breast cancer. J Natl Cancer Inst, 99: 628–638, 2007.
[16] D'Alessio A, De Luca A, Maiello MR, et al. Effects of the combined blockade of EGFR and ErbB-2 on signal transduction and regulation of cell cycle regulatory proteins in breast cancer cells. Breast Cancer Res Treat, 123: 387–396, 2010.
[17] Normanno N, Morabito A, De Luca A, et al. Target-based therapies in breast cancer: current status and future perspectives. Endocr Relat Cancer, 16: 675–702, 2009.
[18] Arteaga CL, O'Neill A, Moulder SL, et al. A phase I-II study of combined blockade of the ErbB receptor network with trastuzumab and gefitinib in patients with HER2 (ErbB2)-overexpressing metastatic breast cancer. Clin Cancer Res, 14: 6277–6283, 2008.
[19] Narayan M, Wilken JA, Harris LN, et al. Trastuzumab-induced HER reprogramming in "resistant" breast carcinoma cells. Cancer Res, 69: 2191–2194, 2009.
[20] Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. J Clin Oncol, 28: 1138–1144, 2010.
[21] Wong KK, Fracasso PM, Bukowski RM, et al. A phase I study with neratinib (HKI-272), an irreversible pan ErbB receptor tyrosine kinase inhibitor, in patients with solid tumors. Clin Cancer Res, 15: 2552–2558, 2009.
[22] Burstein HJ, Sun Y, Dirix LY, et al. Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. J Clin Oncol, 28: 1301–1307, 2010.
[23] Chandarlapaty S, King T, Sakr R, et al. Hyperactivation of the PI3K-AKT pathway commonly underlies resistance to trastuzumab in HER2 amplified breast cancer. Cancer Res, 69(24 Suppl.): Abstract 709, 2009.
[24] Vogel CL, Burris HA, Limentani S, et al. A phase II study of trastuzumab-DM1 (TDM1), a HER2 antibody-drug conjugate (ADC), in patients (pts) with HER2+ metastatic breast cancer (MBC): final results. J Clin Oncol, 27(15S): 45s (Abstract 1017), 2009.