Current therapeutic strategies of anti-HER2 treatment in advanced breast cancer patients

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The *HER2/neu* (*ERBB2*) oncogene is amplified and/or overexpressed in approximately 20% of breast cancers, and is a strong prognostic factor for relapse and poor overall survival, particularly in node-positive patients. It is also an important predictor for response to trastuzumab, which has established efficacy against breast cancer with overexpression or amplification of the HER2 oncogene. Treatment with the anti-HER2 humanized monoclonal antibody – trastuzumab significantly improves progression-free and overall survival among patients with HER2-positive breast cancer. However, in most patients with HER2-positive metastatic breast cancer, the disease progresses occurred, what cause the need for new targeted therapies for advanced disease. In clinical trials, there are tested new drugs to improve the results of treatment for this group of patients. This paper presents new drugs introduced into clinical practice for treatment of advanced breast cancer, whose molecular target are receptors of the HER2 family. In addition, new therapeutic strategies and drugs that are currently in clinical researches are discussed.

Key words: breast cancer, HER2 overexpression, treatment strategy, clinical trials.

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Introduction

The *HER2/neu* (*ERBB2*) oncogene is amplified and/or overexpressed in approximately 20% of breast cancers and is a strong prognostic factor for relapse and poor overall survival (OS), particularly in node-positive patients. It is also an important predictor for response to trastuzumab, which has established efficacy against HER2-positive breast cancer [1]. The presence of *HER2* overexpression and *HER2* gene amplification is associated with a higher degree of malignancy, a high proliferative index, a lower degree of differentiation, a negative steroid receptor status and presence of metastases in the lymph nodes [2–4]. In addition, the increased invasiveness of this type of cancer causes a high risk of CNS metastasis. Treatment with the anti-HER2 humanized monoclonal antibody trastuzumab significantly improves disease-free survival (DFS) (33–52%) and OS (34–41%) in early breast cancer patients [5, 6]. This drug also provides significant clinical benefit in overall response rate (ORR; 50%) and increases OS and time to disease progression in HER2-positive metastatic breast cancer both in monotherapy and in combination with chemotherapy in comparison with chemotherapy alone [7, 8]. However, in most patients with HER2-positive metastatic breast cancer, disease progression occurred, which caused the need for new targeted therapies for advanced disease.

Anti-HER2 therapy has its origin in 1998, when trastuzumab was registered for the first time on the basis of the results of clinical trials [8, 9]. Initially trastuzumab was registered as monotherapy for the treatment of patients with HER2-positive metastatic breast cancer and then in combination with paclitaxel and docetaxel in patients who had not received prior chemotherapy for metastatic disease [10–12]. In the following years, registration was extended to include adjuvant treatment of patients with HER2-positive early breast cancer, after surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy, if it was applied [13, 14]. In 2007 new registration indications appeared, allowing the administration of trastuzumab together with aromatase inhibitors for the treatment of postmenopausal women with positive steroid receptor status who did not receive prior trastuzumab [15]. At the turn of 2012 and 2013 a new generation of drugs such as pertuzumab and TDM-1 were introduced into clinical practice [16–18]. This paper presents the role of new drugs, whose molecular target are receptors of the HER2 family, in clinical practice for treatment of advanced breast cancer patients. In addition, the authors discuss new therapeutic strategies and drugs that are currently researched in clinical trials.

Pertuzumab

Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (subdomain II) of HER2 and thereby blocks ligand-dependent heterodimerization of HER2 with other HER

family members, including EGFR, HER3, and HER4. As a result, it inhibits the signal transduction into the cell proliferation. The drug may be used in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic breast cancer or unresectable local recurrence who have not been treated with anti-HER2 therapy or chemotherapy for metastatic disease [19]. In 2013 pertuzumab was also approved for use in combination with trastuzumab and docetaxel for neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer as part of a complete treatment regimen for early breast cancer [20].

The Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA), registration, phase III study assessed the efficacy and safety of pertuzumab plus trastuzumab and docetaxel in comparison with placebo plus trastuzumab and docetaxel, as a first-line treatment for patients with HER2-positive metastatic breast cancer. In this study 407 adult patients with HER2-positive breast cancer with locally recurrent or metastatic disease received at least one dose of pertuzumab in combination with trastuzumab and docetaxel. The primary end point was progression-free survival (PFS). Secondary end points included overall survival, objective response rate and safety. The study showed an extension of median PFS by 6.1 months (18.4 vs. 12.4) and a 34% reduction in the risk of death in patients treated with pertuzumab in combination with trastuzumab and docetaxel. The median overall survival of patients undergoing therapy with trastuzumab in combination with chemotherapy was more than 3 years (37.6 months).

Currently the median overall survival in patients treated with a regimen containing pertuzumab is 56.5 months. The most frequently reported side effects (> 50%) were diarrhea, epilation and neutropenia. However, the most frequent adverse events of grade 3–4 according to the CTCAE (> 10%) were hematological complications such as neutropenia, febrile neutropenia and leucopenia. Cardiac complications, such as heart left ventricular dysfunction, occurred with an incidence of < 10%, of which 1.2% was symptomatic left ventricular systolic dysfunction [16, 19].

Another study assessing the efficacy of pertuzumab was NEOSPHERE (Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation) trial. This is a multicenter, international, phase II trial in which pertuzumab was used in combination with trastuzumab and docetaxel as neoadjuvant chemotherapy in patients with locally advanced, HER2-positive breast cancer. Four hundred seventeen patients were assigned to four treatment arms, which received: trastuzumab with docetaxel, trastuzumab with pertuzumab and docetaxel, trastuzumab with pertuzumab, and pertuzumab with docetaxel. After four cycles of treatment, the patients underwent surgery, and then systemic therapy was continued in the form of three cycles of chemotherapy with FEC (fluorouracil, epirubicin and cyclophosphamide) in patients who had previously received docetaxel or four cycles of docetaxel followed by three cycles of FEC chemotherapy in patients who had not previously received docetaxel. The primary endpoint was complete pathological remission (pCR) evaluated in the surgical specimen after 12 weeks of neoadjuvant treatment. Secondary end points included clinical response, time to clinical response, operating rate of conservative treatment, safety profile and DFS. Treatment with pertuzumab, trastuzumab and docetaxel chemotherapy significantly improved the rate of total pCR by 16.8% compared to trastuzumab and docetaxel alone (45.8% vs. 29%, $p = 0.0141$). The pCR rates were 29% for trastuzumab and docetaxel, 45.8% for pertuzumab, trastuzumab and docetaxel, 16.8% for pertuzumab with trastuzumab, and 24% for pertuzumab with docetaxel. An increase of cardiotoxicity as a result of the addition of pertuzumab to a treatment regimen with trastuzumab was not observed. The combination of trastuzumab with pertuzumab increases the effectiveness of neoadjuvant therapy, as indicated by the preliminary results of the study [20].

Toxicity of anti-HER2 therapy (pertuzumab in combination with trastuzumab) together with anthracyclines and carboplatin in neoadjuvant treatment was studied in the TRYPHANEA trial. The study included 225 patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer with tumor size of at least 2 cm. The exclusion criteria included the presence of bilateral breast cancer, prior treatment with anthracyclines and radiotherapy, other types of cancer (except basal cell carcinoma and cervical cancer *in situ*), cardiovascular comorbidity and long-term steroid treatment at a dose of > 10 mg. The primary endpoint was cardiotoxicity. Secondary endpoints were the proportion of pCR (estimated after 6 cycles of treatment), treatment toxicity, clinical response rate, PFS, OS and DFS. Patients were randomized to three treatment arms. Patients in arm A received 6 cycles of treatment containing trastuzumab with pertuzumab together with the FEC scheme from the 1st to the 3rd cycle and then with docetaxel from the 4th to the 6th cycle. In arm B the FEC scheme was used for the first three cycles and then pertuzumab with trastuzumab and docetaxel for the next three cycles. In another arm of the study, patients received trastuzumab and pertuzumab in combination with docetaxel and carboplatin. After six cycles of treatment patients were qualified for surgery. Then they received complementary immunotherapy with trastuzumab for one year, completing radiotherapy and hormone therapy, depending on the steroid receptor status. The rates of total pCR in the three arms were as follows: pCR of 61.6% for arm A, 57.3% for arm B and 66.2% for the anthracycline-free arm. Side effects observed in this trial were consistent with those seen in previous studies with pertuzumab. The most common adverse events were neutropenia, leucopenia, febrile neutropenia and diarrhea [21, 22].

TDM-1 (trastuzumab emtansine)

The next new generation drug is TDM-1 (ado-trastuzumab emtansine). Trastuzumab emtansine is an antibody-drug conjugate (ADC), a combination between a monoclonal antibody (trastuzumab) and the chemotherapeutic maytansinoid (emtansine). Trastuzumab links to the HER2 receptor and inhibits the transmission of signals

into the cell. The cytostatic attached to the antibody gets into the cell by endocytosis. Inside the cell the cytostatic is converted by lysosomes to its active metabolite acting at the destination place. Maytansine has not found application in systemic treatment due to high cytotoxicity of the substances and low selectivity towards tumor cells, resulting in serious systemic complications. Only the combination of maytansine with monoclonal antibody can deliver a chemotherapeutic agent directly to the tumor cells and increase the safety of the therapy. This drug has found use in the treatment of patients with HER2-positive metastatic breast cancer (MBC) who have previously received therapy with trastuzumab and taxanes [17]. The basis for the registration of TDM-1 for the treatment of patients with MBC was the phase III EMILIA trial. The study included 991 patients with unresectable, locally advanced or metastatic HER2-positive breast cancer who had previously received trastuzumab with docetaxel. Patients were randomized into two arms: the first with TDM-1 (495 patients) and the second with capecitabine and lapatinib (496 patients). The primary endpoints were OS and PFS. Secondary endpoints were: one- and two-year survival rate, safety profile, objective response rate, duration of response and quality of life. A 35% reduction in the risk of progression in the group receiving TDM-1 was observed. Median progression-free survival was 9.6 months in patients receiving TDM-1 and 6.4 months in patients treated with lapatinib plus capecitabine ($p < 0.00001$). An improvement in overall survival (30.9 vs. 25.1 months) for patients receiving TDM-1 was also detected. TDM-1 therapy was also burdened with lower rates of complications in grade three or higher toxicity (40% vs. 57%). The most common side effects of TDM-1 of grade 3-4 were increase in transaminases, thrombocytopenia and anemia [23].

At the moment, other studies on the effectiveness of TDM-1 are ongoing: the multicenter, randomized phase III study MARIANNE and the TH3RESA trial. The MARIANNE study evaluates the efficacy and toxicity of TDM-1 treatment in combination with pertuzumab or with placebo in comparison with therapy with trastuzumab and taxanes (docetaxel or paclitaxel). The study includes patients with HER2 overexpression with disease progression, recurrence of locally advanced breast cancer or patients not treated previously due to disease metastases. The primary endpoints of the study include progression-free survival and side effects of therapy. Secondary endpoints of the study are: annual survival rate, OS, IFR (the time at which treatment failure can be pronounced), objective response rate, clinical benefit, duration of response and overall survival period of 2 years. Early results are expected by 2014 [24].

TH3RESA is a randomized, multicenter, two-arm, open-label study which evaluates the efficacy and safety of trastuzumab emtansine (T-DM1) in comparison with treatment of the physician's choice in patients with metastatic or unresectable locally advanced/recurrent HER2-positive breast cancer. The primary endpoints of the study include PFS and OS. Secondary endpoints of the study are: objective response rate, duration of objective response, treatment safety and quality of life. Primary results from the TH3RESA trial were reported at the 2013 European Cancer Congress. Patients treated with T-DM1 had a median PFS of 6.2 months vs. 3.3 months in the control arm (hazard

Table 1. Summary of clinical trials

		Number of patients	Median PFS months	Median OS months	pCR
CLEOPATRA phase III study	P + H + T vs. placebo plus H + T	808	18.4 vs. 12.4	not reached vs. 37.6	NA
TRYPHANEA phase II study	FEC + H + P ×3 → T + H + P ×3; FEC ×3 → T + H + P ×3; T + CBDCA + H + P ×6	225	NA	NA	61.6% vs. 57.3% vs. 66.2%
NEOSPHERE phase II trial	H + T vs. H + P + T vs. H + P vs. P + T	417	NA	NA	29% vs. 45.8% vs. 16.8% vs. 24%
EMILIA phase III trial	TDM-1 vs. X + L	991	9.6 vs. 6.4	30.9 vs. 25.1	NA
TH3RESA trial	T-DM1 vs. treatment of physician's choice	600	6.2 vs. 3.3	not reached vs. 14.9	NA

H – trastuzumab; P – pertuzumab; T – docetaxel; FEC – 5-fluorouracil, epirubicin, cyclophosphamide; CBDCA – carboplatin; X – capecitabine; L – lapatinib; NA – not applicable

Table 2. Summary of cardiotoxicity in clinical trials

		Asymptomatic cardiotoxicity	Symptomatic cardiotoxicity (grades > 3)
CLEOPATRA phase III study	P + H + T vs. placebo + H + T	4.4% vs. 8.3%	1% vs. 1.8%
EMILIA phase III study	TDM-1 vs. X + L	1.7% vs. 3.3%	0.2% vs. 0.4%
TRYPHANEA phase II study	FEC + H + P ×3 → T + H + P ×3; FEC ×3 → T + H + P ×3; T + CBDCA + H + P ×6	5.6% vs. 5.3% vs. 3.9%	0% vs. 2.7% vs. 0%

H – trastuzumab; P – pertuzumab; T – docetaxel; FEC – 5-fluorouracil, epirubicin, cyclophosphamide; CBDCA – carboplatin; X – capecitabine; L – lapatinib

ratio = 0.528; 95% CI: 0.422–0.661; $p < .0001$). Median OS was 14.9 months in the control arm but has not yet been reached in the T-DM1 arm. Adverse events of grade 3 or higher were more frequent in the control arm: 43.5% vs. 32.3% in the T-DM1 arm. The rate of cardiac events was low in both arms: left ventricular ejection fraction (LVEF) < 50 was reported in 1.1% and 1.5%, respectively. Final results are expected in 2015 [25]. A summary of the clinical trials and cardiac side effects in clinical studies are shown in Tables 1 and 2.

Subcutaneous form of trastuzumab in the treatment of HER2 (+) breast cancer

A new strategy for anti-HER2 therapy means not only new forms of drugs, but also new ways of trastuzumab administration (subcutaneous form). In the international, randomized phase III HannaH trial, pharmacokinetics of the subcutaneously administered drug, its efficacy and safety were evaluated in relation to the drug administered intravenously. The study involved patients with locally advanced or inflammatory breast cancer who received eight cycles of neoadjuvant chemotherapy with trastuzumab. Two hundred ninety-nine patients were treated with intravenous trastuzumab and 297 with a subcutaneous injection. Chemotherapy consisted of four cycles of docetaxel alone and then four cycles of treatment according to the CMF regimen (5-fluorouracil 600 mg/m^2, methotrexate 40 mg/m^2, cyclophosphamide 100 mg/m^2). After eight cycles, patients underwent surgery. Immunotherapy was then continued for a period of one year. Patient preferences, safety, pharmacokinetics, and event-free survival were evaluated. The study showed that in terms of pharmacokinetics, safety and efficacy of the subcutaneous form of trastuzumab are not inferior to the intravenous form [26].

The carrier for the drug is a recombinant human hyaluronidase (rHuPH20) which does not affect the effect of the treatment, and its local influence on tissue is fully reversible within 24 hours. A single subcutaneous dose of trastuzumab was 600 mg in a volume of 5 ml administered within 5 min. The dose does not require the conversion of patient body weight and also does not require a loading dose of trastuzumab. The dose is the same during the entire treatment period.

Concurrent administration of trastuzumab with anthracyclines

Neoadjuvant therapy is a standard treatment in patients with locally advanced, inflammatory, or inoperable primary breast cancer. Addition of trastuzumab to neoadjuvant chemotherapy in *HER2*-positive breast cancer has been investigated in a number of trials [27, 28]. The use of concurrent therapy has increased the pCR rate up to 75% with no significant increase in cardiotoxicity. Buzdar *et al*. evaluated 282 patients with HER2-positive breast cancer. One hundred and forty of them received sequential treatment with fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2 for four cycles followed by paclitaxel 80 mg/m^2 and trastuzumab 2 mg/kg once per week for 12 weeks. The concurrent treatment group received paclitaxel and trastuzumab once per week for 12 weeks followed by four cycles of FEC-75 and once-weekly trastuzumab, in the same doses as the sequential group. The primary end point was the percentage of patients who had a pathological complete response, which was described in 78 of 138 patients who received sequential treatment and in 77 of 142 who received concurrent treatment. This study has shown that concurrent administration of trastuzumab with anthracyclines does not provide additional benefits [29]. Sequential anthracycline-taxane-based chemotherapy in combination with trastuzumab is considered safe therapy for HER2-positive breast cancer in neoadjuvant therapy.

mTOR inhibitors for treatment of HER2 (+) breast cancer

One of the mechanisms of resistance to trastuzumab is an increase in activation of the PI3K/AKT/mTOR pathway. Activation of the PI3K pathway results from a decrease or loss of PTEN activity, or an activating mutation of the catalytic domain of PI3K (PIK3CA) is responsible for the resistance to trastuzumab [30]. The results of phase I and II trials indicate a possibility of cells' resensitization to trastuzumab after using an oral inhibitor of the mTOR pathway (everolimus). The BOLERO-1 study is an international, multi-center phase III clinical trial, which enrolled 719 patients with locally advanced breast cancer or metastatic cancer who had not received previous chemotherapy. Patients were assigned to a treatment group receiving everolimus therapy with paclitaxel and trastuzumab or to a control group receiving therapy with trastuzumab and paclitaxel with placebo (2 : 1). The primary endpoint is the time of progression-free survival. Overall survival, response rate and the degree of clinical improvement are defined as secondary endpoints. This study is ongoing. In the phase II clinical trial in patients receiving everolimus together with trastuzumab and paclitaxel, the period of progression-free survival was 5.5 months and median overall survival 18.1 months. The most common adverse events of grade 3 or 4 were neutropenia (25.5% grade 3, 3.6% grade 4), inflammation of the oral mucosa (20%), anemia (7.3% grade 3), diarrhea (5.5%), nausea (5.5%) and vomiting (5.5%) [31].

The recently completed study BOLERO-3 showed that the inhibition of mTOR in combination with trastuzumab and vinorelbine therapy significantly improved PFS in comparison with trastuzumab with vinorelbine in patients with metastatic breast cancer [32].

Drugs in clinical trials

Ertumaxomab

Ertumaxomab is a new recombinant monoclonal antibody targeting the HER2 receptor. This antibody is linked with the CD3 antigen located on T cells, with the HER2 receptor located on tumor cells, and also with some FcyR$^+$ antigen presenting cells (macrophages, dendritic cells, NK cells). This leads to the activation of cytotoxic T lymphocytes against aggregation with a T cell/tumor cell. Ertumaxomab and trastuzumab recognize two different HER2/neu epitopes. This drug may provide new treatment oppor-

tunities for HER2-positive breast cancer patients, independent of the expression profile. At present, phase I/II clinical trials are being conducted to evaluate efficacy, tolerability and safety of ertumaxomab in patients with solid tumors with HER2 overexpression after progression on standard systemic treatment. Results are in preparation [33, 34].

Neratinib

Neratinib (HKI-272) is an irreversible inhibitor of tyrosine kinase ErbB. Phase II trials have shown that the combination of neratinib together with paclitaxel in breast cancer patients is associated with a higher response rate in comparison with paclitaxel alone [35]. In the next trial phase I/II efficacy of neratinib (240 mg/day) in combination with capecitabine (1.500 mg/m^2 per day) was evaluated in patients with locally advanced breast cancer or metastatic cancer with progression after treatment containing trastuzumab with taxanes. The results indicate the acceptable toxicity of the used combination (neratinib with capecitabine). The most frequently observed complication was diarrhea, which was observed in 28% of patients. The median PFS was 40.3% for patients who had not received prior lapatinib and 35.9% in patients who were treated with lapatinib [36]. The combination of neratinib (240 mg) with vinorelbine (25 mg/m^2) also showed efficacy in patients with metastatic breast cancer. The percentage of OR was 41% in patients who did not receive prior lapatinib and 8% in patients previously treated with lapatinib [37]. In the next phase II trial, neratinib monotherapy (240 mg/d) was compared with lapatinib (1250 mg/d) plus capecitabine (2000 mg/m^2) therapy in respect of PFS, OS, objective response and clinical benefit rate. Median PFS for neratinib was 4.5 months vs. 6.8 months for lapatinib plus capecitabine, and median overall survival was 19.7 months vs. 23.6 months. The objective response rate (29% vs. 41%; $p = 0.067$) and clinical benefit rate (44% vs. 64%; $p = 0.003$) were lower for the neratinib arm but consistent with previously reported results. This study confirmed clinical activity and tolerability of neratinib in patients with recurrent HER2-positive advanced breast cancer [38].

Afatinib

Afatinib (BIBW 2992) is an irreversible inhibitor of the erbB receptor family. It inhibits signal transduction mediated by activity of all receptor kinases belonging to the ErbB family, involved in growth and spread of tumors. Now several clinical trials are being conducted to evaluate the efficacy and safety profile of afatinib. In the study LUX-Breast-2 the efficacy and safety of afatinib used in monotherapy (40 mg per day), with paclitaxel (80 mg/m^2 per week) or with vinorelbine (25 mg/m^2) in patients with metastatic breast cancer were compared. Patients received monotherapy with afatinib, afatinib with vinorelbine or a drug of the researcher's choice. The primary endpoints of therapeutic benefit were absence of metastases in the central nervous system, lack of progression occurring changes, and lack of neurological symptoms. Secondary endpoints were PFS and OS. Results of the study are in preparation [39].

Heat shock protein 90

Heat shock protein 90 (Hsp 90) is a molecular chaperone required for stability and function of signaling proteins that promote cancer cell growth and/or survival. Heat shock protein 90 small molecule inhibitors interact with a single molecular target, thus promoting the destabilization and eventual degradation of cancer cell survival and growth-promoting proteins. These inhibitors have shown promising anti-tumor activity in preclinical breast cancer trials. Some clinical studies have shown that trastuzumab refractory HER2-positive breast cancers are sensitive to inhibition of Hsp 90 [40]. One Hsp 90 inhibitor is retaspimycin hydrochloride, which has antiproliferative and antineoplastic activities. The efficacy of retaspimycin in combination with trastuzumab in advanced HER2-positive metastatic breast cancer after progression on trastuzumab therapy was evaluated in phase II clinical trials. Retaspimycin HCL at a dose of 300 mg/m^2 weekly was used together with 6 mg/kg trastuzumab every 3 weeks. Primary endpoints were overall response (ORR), safety and tolerability. The best response was disease stagnation observed in 62% of patients. Treatment side effects were detected in about 5% of patients. The most frequent toxic effects were fatigue and nausea, and diarrhea of CTCAE grade 1 or 2 [41]. Further trials are warranted.

Summary

Overexpression of HER2 is an important prognostic and predictive factor in breast cancer patients. The use of anti-HER2 therapy has improved the prognosis and has caused longer survival in this group of patients. The new drugs provide a more complete blockade of the HER2 receptor. Combination of immunotherapy with chemotherapy leads to more precise delivery of the chemotherapeutic agent to the targeted tumor cells and thereby causes minimization of treatment complications. In clinical trials, there are being tested many new molecules whose aim is to improve the results of patients' treatment with HER2-overexpression.

The authors declare no conflict of interest.

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