[Frontiers in Bioscience S4, 31-42, January 1, 2012]

Which role for EGFR therapy in breast cancer?

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1. ABSTRACT

EGFR and HER2 are highly expressed in 15-30% of breast cancer tissues. Therefore, EGFR and its downstream signaling pathways are promising anti-tumour targets. HER2 overexpression is often associated with estrogen receptor (ER) and progesterone receptor (PR) negativity, high histological grade, high rates of cell proliferation and lymph node involvement. Moreover, it is correlated with disease aggressiveness, increased rates of recurrence and poorer survival in node-positive breast cancer patients, whereas the prognostic significance in patients with node-negative tumors remains somewhat controversial. This paper focuses on the therapeutic strategy for treatment of HER2 overexpressing breast cancer in advanced stages of disease, as well as in the adjuvant and neo-adjuvant settings.

2. INTRODUCTION

Her-2/neu (also known as c-erbB2 or ERBB2) is a proto-oncogene located on chromosome 17. It encodes a trans-membrane growth factor receptor with tyrosine kinase activity. Overexpression and/or amplification of Her-2/neu is detected in approximately 20% to 30% of invasive ductal carcinomas of the breast (1-4). It has been well documented that overexpression and/or amplification of Her-2/neu is associated with poor prognosis (1, 5-7). Patients with increased expression of Her-2/neu also show a poorer response to non-anthracycline containing cytotoxic (8-11) and hormonal therapies (12-14).

In recent years, researchers developed treatments for breast cancer that specifically target HER2. Trastuzumab is a humanized monoclonal antibody that

targets the extracellular domain of the protein encoded by the HER2/neu gene. In 1998, after the demonstration of significant survival benefit, the US Food and Drug Administration (FDA) approved trastuzumab as first-line treatment, in combination with paclitaxel, for women with metastatic HER2/neu-positive breast cancer (15). Thereafter, lapatinib a new inhibitor of tyrosine kinase activity of both HER1 (EGFR) and HER2 receptors, demonstrated clinical activity in the treatment of metastatic breast cancer, in patients who did not respond to treatment with trastuzumab. In late 2007, the FDA approved the combination of capecitabine plus lapatinib for the treatment of patients progressing on prior chemotherapy regimens and trastuzumab (16).

3.HER2-TARGETED AGENTS IN THE METASTATIC SETTING

3.1.Trastuzumab monotherapy

The first phase II study to assess the efficacy and safety of this agent in the treatment of HER2-overexpressing metastatic breast cancer, was carried out in 1996 (17). In this study, 46 patients who had received extensive chemotherapy for metastatic breast cancer were treated with trastuzumab intravenously (a loading dose of 250 mg, then 100 mg/week). An overall response rate of 11.6% (5 of 43 assessable patients) was obtained, with 1 patient achieving a complete response. This study was followed by a larger single-arm trial, in which 222 patients with HER2-overexpressing metastatic breast cancer were enrolled (18). In this study, patients received a loading dose of 4 mg/kg intravenously followed by 2 mg/kg, administered weekly. Complete response was observed in 8 (4%) patients, and partial response in 26 (12%) patients, respectively.

The efficacy of single-agent trastuzumab in patients with HER2+ breast cancer was confirmed in subsequent trials, including one in which patients were randomized to 2 different doses of trastuzumab: a 4 mg/kg loading dose followed by 2 mg/kg weekly, or an 8 mg/kg loading dose followed by 4 mg/kg weekly (19). Efficacy was similar between the two treatment arms. Furthermore, the results from this trial established the value of Fluorescent In-Situ Hybridization (FISH) as a method for selecting patients for therapy with trastuzumab: responses were seen in 34% of patients who were HER2+ by FISH, and 7% in those who were HER2– by FISH (19). A subsequent study was designed to assess whether trastuzumab would be effective and safe if administered every 3 weeks, instead of every week (20). Although this was not a randomized trial, the response rate in this study (19 of 83 (23%) patients) was similar to those of previous studies with trastuzumab in monotherapy. These trials validated the efficacy of trastuzumab in monotherapy and suggested the doses and weekly or 3-weekly dosing schedules as appropriated.

3.2.Chemotherapy in combination with trastuzumab

Slamon *et al* compared responses in patients who received chemotherapy plus trastuzumab with those who received chemotherapy alone in HER2-overexpressing metastatic breast cancer (15). In this study, chemotherapy consisted of an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide for patients who had not received prior anthracycline, or paclitaxel but who previously had received adjuvant anthracycline therapy. Analysis of the entire patient cohort, as well as the 2 chemotherapy treatment groups, showed that addition of trastuzumab to chemotherapy resulted in longer progression-free survival (PFS) (median PFS in the entire cohort: 7.4 months for the trastuzumab plus chemotherapy arm compared to 4.6 months for the chemotherapy alone arm; $P<0.001$) and longer overall survival (OS) (median OS in the entire study population: 25.1 months for the trastuzumab plus chemotherapy arm *vs* 20.3 months in the chemotherapy alone one, with a 20% reduction in the relative risk of death; $P=0.046$), as well as a higher overall response rate (ORR, 50% *vs* 32% for chemotherapy alone; $P<0.001$). In a subsequent study, patients with HER2+ metastatic breast cancer (MBC) were randomly assigned to receive docetaxel (100 mg/m^2 every 3 weeks) with or without trastuzumab (a 4 mg/kg loading dose followed by 2 mg/kg weekly) (21). Trastuzumab plus docetaxel was significantly superior to docetaxel alone, in terms of ORR (61% *vs* 34%, respectively; $P=0.0002$), OS (31.2 *vs* 22.7 months, respectively; $P=0.0325$), duration of response (median 11.7 *vs* 5.7 months, respectively; $P=0.009$), and time-to-progression (TTP, median 11.7 *vs* 6.1 months, respectively; $P=0.0001$). Taxanes have been further studied (22-24); while the association of trastuzumab with vinorelbine also produced response rates that are often over 60% (25-27). Responses are always at the highest rates in those patients who have Immune-Histo-Chemistry (IHC) 3+ or FISH+ test results. The results of a randomized phase III trial comparing vinorelbine plus trastuzumab versus docetaxel plus trastuzumab were recently published (28). In this trial, 284 patients with HER2-positive MBC not previously treated with chemotherapy, were randomized and followed for a median time period of 2.5 years. The docetaxel regimen was associated with a significant higher overall incidence of grade 3-4 toxicity (81% *vs* 51%, $P<0.0001$). The ORR was 59.3% in both groups, but patients on vinorelbine arm remained on therapy significantly longer, reflecting in a median time to treatment failure of 7.7 months versus 5.6 months with docetaxel (hazard ratio (HR) 0.50, 95% CI 0.38-0.64, $P<0.0001$). Median OS for vinorelbine treated patients was 39 months *vs* 36 months with docetaxel, a non significant difference.

Other agents that have been successfully combined with trastuzumab include gemcitabine (29) and capecitabine (30). Despite the known association of cardiac toxicity with anthracycline-containing regimens, studies are in progress using liposome-encapsulated doxorubicin (31) and epirubicin (32) in combination with trastuzumab.

Of great interest is the combination of trastuzumab with platinum and taxane. Pegram *et al* (33) demonstrated a 24% rate of response and a 48% rate of clinical benefit in chemoresistant HER2-positive breast cancer using trastuzumab plus cisplatin. Since then, tolerance and toxicity concerning cisplatin have stimulated

evaluation of carboplatin-taxane doublets administered either weekly (34) or every 3 weeks. As examples, investigators at UCLA (35) have evaluated a combination of docetaxel plus carboplatin given every 3 weeks together with weekly trastuzumab. Among patients who were FISH+, there was a 64% ORR (complete plus partial responses) to that combination in comparison to a 41% rate for those who were FISH-. A US Oncology group enrolled 196 patients with metastatic breast cancer who were HER2 2+, 3+ on IHC or FISH+ (36) for comparing paclitaxel given every 3 weeks plus weekly trastuzumab vs paclitaxel plus carboplatin given every 3 weeks plus weekly trastuzumab. The combination arm was more toxic but provided longer responses than the paclitaxel/trastuzumab-alone arm. These data warrant trials to evaluate this approach for adjuvant therapy in high-risk breast cancer patients.

More recently, it was reported an interesting prospective trial called HERCULES which combined a phase I dose-finding stage, with a phase II randomized stage (37). In total, 120 patients with HER2-positive MBC and adequate cardiac function received first-line trastuzumab (4 mg/kg intravenous loading dose, then 2 mg/kg weekly) plus cyclophosphamide (600 mg/m^2) and epirubicin either 60 mg/m^2 (HEC-60) or 90 mg/m^2 (HEC-90) for six cycles, followed by trastuzumab until progression. Sixty patients with HER2-negative disease received epirubicin (90 mg/m^2) and cyclophosphamide (EC-90) alone. The primary end point was dose-limiting cardiotoxicity (DLC). Incidence of DLC was 5%, 1.7%, and 0% in the HEC-90, HEC-60, and EC-90 arms, respectively. All DLC events were manageable. There were no cardiac-related deaths. Other adverse-event profiles were comparable across the three arms, except for febrile neutropenia, which was reported in 10% of the HEC-90 arm compared with 3% of the other arms. Tumor ORRs were 57%, 60%, and 25% in the HEC-60, HEC-90, and EC-90 arms, respectively; median TTP was 12.5, 10.1, and 7.6 months, respectively.

With regard to hormone-sensitive breast cancer, in the TAnDEM study, postmenopausal women with HER2+ and ER- and/or PR-positive metastatic breast cancer were randomly assigned to receive anastrozole plus trastuzumab or anastrozole alone (38). Median PFS was longer in the combination arm (4.8 months vs 2.4 months; P=0.0016), as well as TTP (4.8 vs 2.4 months, respectively; P=0.0007). No significant difference was seen in OS (28.5 months vs 23.9 months, respectively; P=0.325), but we have to consider that 70% of patients in the anastrozole alone arm crossed over to receive trastuzumab after progression on anastrozole.

3.3. Lapatinib trials in first-line therapy

Lapatinib is an orally active small molecule that inhibits the tyrosine-kinase (TK) activity of both HER1 (EGFR) and HER2. In preclinical studies, lapatinib was not cross-resistant with trastuzumab (39-41).

Lapatinib (Figure 1)) competes with the binding of ATP to the intracellular tyrosine kinase domain of membrane receptors thereby inhibiting receptor auto-phosphorylation and blocking downstream signal transduction of both the Ras/Raf mitogen-activated protein kinases (MAPKs) and the PI3K (phosphatidilinositol-3-kinase)/Akt pathways, leading to an increase in apoptosis induction and decreased cellular proliferation (42, 43)

There are several theoretical advantages with a small molecule inhibiting both HER1 and HER2 compared to a monoclonal antibody that targets only the extracellular domain of ErbB-2. First of all, an inhibitor of just one TK activity might not be enough effective in inhibiting heterodimers containing both HER1 and HER2 (44). An important additional theoretical advantage of the dual kinase inhibitor as lapatinib over trastuzumab is related to the occurrence, in some tumors, of truncated forms of both HER1 and HER2 lacking their extracellular domain, thus the antibodies targeting the external domains of such truncated forms of receptors would fail to recognize them

Lapatinib is currently approved, in combination with capecitabine, for the treatment of advanced or metastatic HER2+ breast cancer after prior therapy with anthracycline, taxane, and trastuzumab. A recent phase III trial evaluated the efficacy and safety of paclitaxel (175 mg/m^2 every 3 weeks) plus lapatinib (1500 mg/day) or placebo, in the first-line setting (45). In this study, patients with HER2+ metastatic breast cancer showed longer TTP in the lapatinib arm vs the placebo arm (median 36.4 vs 25.1 weeks; P=0.005), as well as longer event-free survival (median 35.1 vs 21.9 weeks; P=0.004) and increased ORR (63.3% vs 37.8%; P=0.023) (46).

Another trial tested lapatinib combined with first-line aromatase inhibitor therapy (letrozole) in metastatic breast cancer. In this trial, patients with hormone receptor–positive breast cancer were randomly assigned to receive letrozole (2.5 mg/day) plus lapatinib (1500 mg/day) or letrozole plus placebo. Again, the clearest evidence for treatment efficacy was found in the HER2+ subset (47) .

3.4.HER2-targeted agents after progression on trastuzumab

Despite the significant efficacy of trastuzumab in patients with HER2+ metastatic breast cancer, almost all patients experienced disease progression while on trastuzumab therapy. A number of clinical studies have been carried out to evaluate treatment strategies beyond progression on trastuzumab. In one study, patients who had progressed on trastuzumab were randomly assigned to receive capecitabine (2500 mg/m^2, on days 1 to 14 of a 3-week cycle) with or without trastuzumab (6 mg/kg, every 3 weeks) (48). Although this study was closed before full patients accrual, treatment with the combination regimen resulted in a significant improvement than the capecitabine alone arm in terms of TTP (8.2 vs 5.6 months; P=0.0338) and ORR (48.1% vs 27.0%; P=0.0115) but no significant change in OS was seen (25.5 vs 20.4 months; P=0.2570).

As described above, lapatinib has also demonstrated efficacy as a second-line treatment in patients with HER2+ metastatic breast cancer, and trials have been carried out to assess its activity either as monotherapy or in

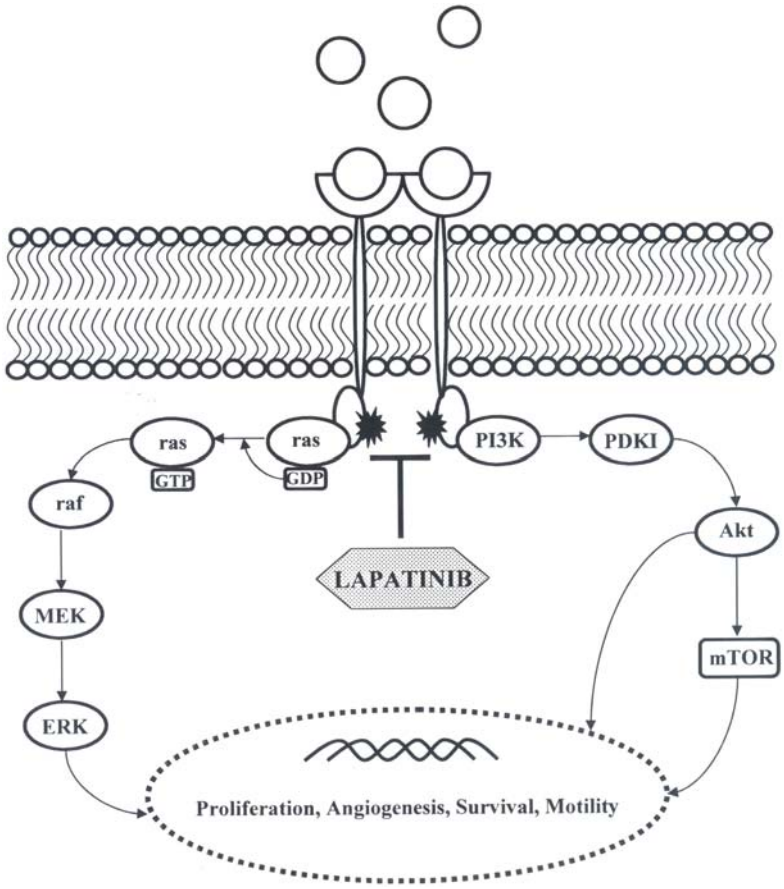

Figure 1. Lapatinib binds to the tyrosine kinase (TK) domain, competitively blocking ATP binding, thus inhibiting the downstream cascade of events

combination with other agents in patients with HER2+ advanced or metastatic breast cancer, whose tumor has progressed on trastuzumab therapy. The study, that led to the approval of lapatinib, examined capecitabine (2000 mg/m^2/day, on days 1 to 14 of a 3-weekly cycle) plus lapatinib (1250 mg/day) vs capecitabine plus placebo and demonstrated an increase in median TTP (8.4 vs 5.6 months; P=0.0338) and ORR (48.1% vs 27.0%; P=0.0115) but no significant change in OS (25.5 vs 20.4 months; P=0.2570) (16, 49).

However, some studies concerning the efficacy of lapatinib in monotherapy in patients who had disease progression on prior therapy, including chemotherapy and trastuzumab, showed modest effectiveness in patients with HER2+ disease (50).

In one study, an ORR of 4.3% (by investigator review, 1.4% by independent review) was achieved. A more recent study on lapatinib in monotherapy (1250 or 1500 mg/day), in patients whose cancer had progressed on trastuzumab therapy, demonstrated the clinical benefit of lapatinib in this patients population (51). Clinical benefit rates (consisting of complete response plus partial response plus stable disease for ≥24 weeks) were 14.1% by investigator review, and 9% by independent review.

In another study, patients whose disease had progressed on trastuzumab therapy were treated with lapatinib (1500 mg/day), or lapatinib (1000 mg/day) plus trastuzumab (4 mg/kg loading dose followed by 2 mg/kg doses every week) (52). Improved efficacy was seen in the combination treatment arm, in terms of median PFS (12.0 vs 8.1 weeks with lapatinib alone; HR=0.73, P=0.008; with a 6-months PFS of 28% vs 13%). Median OS was 51.6 weeks in the combination arm, and 39 weeks in the lapatinib alone arm (P=0.106). ORRs were not significantly different between the treatment arms, being equal to 10.3% in the combination arm and 6.9% in the lapatinib arm (P=0.46), thus, demonstrating a potential persistent efficacy of trastuzumab despite prior progression on this agent.

4.HER2-TARGETED AGENTS IN THE ADJUVANT SETTING

The effectiveness of trastuzumab plus chemotherapy while increasing prolonged survival in patients with HER2-positive metastatic breast tumors has generated great interest in the adjuvant arena. The largest currently active trials are summarized in Table 1. The National Surgical Adjuvant Breast and Bowel Project trial B-31 (NSABP B-31) and the North Central Cancer Treatment Group trial N9831 (NCCTG N9831) were

Table 1. Phase III clinical trials investigating HER2-targeted agents in the adjuvant setting

Trial	Population	Trial design	End points
NCCTG N9831 (clinicaltrials.gov identifier: NCT00005970)	N+ HER2+ BC	ACx4 → ARM A: PTX qw x12 → ARM B: PTX qw x12 → T qw x52 → ARM C: PTX qw + T qw x12 (+ RT/HT) → T qw x40	Primary: DFS Secondary: OS Tertiary: whether higher levels of ECD or autoAbs to HER2/HER1 are prognostic for DFS & OS; whether concordance of HER2-overexpression correlates with DFS & OS
NSABP B-31 (clinicaltrials.gov identifier: NCT00004067)	N+ HER2+ BC	ACx4 → ARM A: PTX q3w x4 → ARM B: PTX q3w x4 + T qw x52 (in both arms TAM if ER+ and or PR+ BC)	Primary: DFS Secondary: OS
BCIRG 006 (clinicaltrials.gov identifier: NCT00021255)	N+ or high-risk N- HER2+ BC	ARM A: ACx4 → TXT q3w x4 ARM B: ACx4 → TXT q3w x4 + T qw x52 ARM C: TCH x6 + T qw x52	Primary: DFS Secondary: OS
HERA (clinicaltrials.gov identifier: NCT00045032)	N+ or high-risk N- HER2+ BC	Any (neo-)adjuvant CT and adjuvant HT/RT → ARM A: T q3w for up to 1 year → ARM B: T q3w for up to 2 years → ARM C: Observation	Primary: DFS, RFS, DDFS, cardiac toxicity; safety & tolerability Secondary: OS, TTR, TTDR
ALTTO (clinicaltrials.gov identifier: NCT00490139)	N+ or high-risk N- HER2+ BC	ARM A: T q3w for up to 1 year ARM B: L daily for up to 1 year ARM C: T qw x12-18 wks → 6 wks wash-out → L daily x28-34 wks ARM D: T q3w + L daily up to 1 year	Primary: DFS Secondary: TTR, TTDR, incidence of brain metastases, safety & tolerability, OS, biomarkers

Abbreviations: N+, node positive; BC, breast cancer; qw, weekly; wks, weeks; RT, radiation therapy; HT, hormonal therapy; DFS, disease-free survival; OS, overall survival; ECD, extracellular domain; autoAbs, autoantibodies; q3w, every three weeks; TAM, tamoxifen; ER+, estrogen receptor-positive; PR+, progesterone receptor-positive; RFS, relapse-free survival; DDFS, distant disease-free survival; TTR, time-to-recurrence; TTDR, time-to-distant-recurrence; Chemotherapy Schedules: AC, doxorubicin 60 mg/m^2 + ciclophosphamide 600 mg/m^2 every 3 weeks; PTX qw, paclitaxel 80 mg/m^2 weekly; T qw, trastuzumab 4 mg/kg loading dose then 2 mg/kg weekly; PTX q3w, paclitaxel 175 mg/m^2 every 3 weeks; TXT q3w, docetaxel 100 mg/m^2 every 3 weeks; TCH, docetaxel 75 mg/m^2 + carboplatin AUC 6 mg/ml x min every 3 weeks + trastuzumab 4 mg/kg loading dose then 2 mg/kg weekly; T q3w, trastuzumab 8 mg/kg loadiong dose then 6 mg/kg every 3 weeks

designed to examine the efficacy of chemotherapy with or without trastuzumab in patients with operable HER2+ breast cancer (53). In the NSABP B-31 trial, patients were randomly assigned to receive doxorubicin (60 mg/m^2 every 3 weeks) and cyclophosphamide (600 mg/m^2 every 3 weeks), each for 4 cycles, followed by 175 mg/m^2 of paclitaxel every 3 weeks for 4 cycles, or the same regimen plus trastuzumab (4 mg/kg loading dose, given with the first dose of paclitaxel, followed by 2 mg/kg doses given every week for 51 weeks). In the NCCTG N9831 study, the same regimen of doxorubicin and cyclophosphamide was used, but it was followed by weekly paclitaxel (80 mg/m^2 every week for 12 weeks) in one treatment arm. While patients in a second treatment arm received the same chemotherapy regimen followed by trastuzumab (a loading dose of 4 mg/kg followed by 2 mg/kg weekly doses for 51 weeks). Moreover, patients in the third treatment arm received the same chemotherapy regimen plus trastuzumab (a loading dose of 4 mg/kg followed by 2 mg/kg weekly doses for 51 weeks) beginning with the first dose of paclitaxel. A joint analysis of these studies demonstrated a clinical benefit for patients in the trastuzumab treatment arms. Disease-free survival (DFS) at 4 years was 85.3% in the trastuzumab arms vs 67.1% in the control arms (P<0.0001). OS at 4 years was 91.4% in the trastuzumab treatment arms vs 86.6% in the control arms (P=0.015). Significant benefit was also seen in terms of time-to-recurrence, time-to-distant-recurrence, and death from breast cancer. In the most recent results from the NCCTG trial (54), DFS with 50% of planned events (recurrences) were analyzed for the 1,903 patients in arms B (sequential) and C (concurrent). Median follow-up was 5.3 years. There was a 4.4% reduction in the likelihood of recurrence favoring arm C (concurrent trastuzumab with paclitaxel) compared with arm B (sequential use of trastuzumab after chemotherapy; HR 0.77; P=0.0190). Given that the NSABP B-31 trial also employed concurrent use of trastuzumab plus paclitaxel, Dr Perez showed the combined results of arm C with NSABP experimental group, compared with both non-trastuzumab-containing arms (i.e., AC-T alone). With three-year median follow-up, there was a 52% reduction in the annual odds of recurrence with the concurrent approach compared with not using trastuzumab (HR, 0.48: 95% CI, 0.41-0.57; P<0.00001) and a 35% reduction in death as well (HR, 0.65; 95% CI, 0.51-0.84; P=0.0007).

The BCIRG 006 trial is a randomized study to compare three treatment regimens: doxorubicin (60 mg/m^2 every 3 weeks) plus cyclophosphamide (600 mg/m^2 every 3 weeks) for 4 cycles, followed by docetaxel (100 mg/m^2 every 3 weeks for 4 cycles) (AC→T); the same chemotherapy regimen followed by 1 year of trastuzumab (beginning with the first cycle of docetaxel) (AC→TH); or docetaxel (75 mg/m^2 every 3 weeks for 6 cycles) plus carboplatin (AUC6 every 3 weeks for 6 cycles) plus 1 year of trastuzumab (TCH) (55). A disease-free survival benefit was seen in both trastuzumab-containing treatment arms relative to the AC→T arm (AC→TH HR 0.49; TCH HR 0.61). In the FinHer trial, women with node-positive or high-risk node-negative breast cancer were randomly assigned to receive docetaxel (100 mg/m^2 on day 1 of a 21-

day cycle) or vinorelbine (25 mg/m^2, on days 1, 8, 15 of a 21-day cycle), followed by 3 cycles of 5-fluorouracil (600 mg/m^2)/epirubicin (60 mg/m^2)/ cyclophosphamide (600 mg/m^2) (FEC) on day 1 of a 21-days cycle (in both treatment arms) (56). Women who had verified HER2+ cancer were randomly assigned to receive trastuzumab (9 infusions administered at 1-week intervals, beginning on day 1 of the first docetaxel or vinorelbine cycle, a loading dose of 4 mg/kg, followed by subsequent doses of 2 mg/kg) or no trastuzumab. Trastuzumab was not given during FEC administration. An analysis of data from patients with HER2+ cancer showed that the addition of trastuzumab to these chemotherapy regimens provided clinical benefit in this patient group. Kaplan-Meier estimates of recurrence-free at 3 years were 89.3% in the trastuzumab arms and 77.6% in the no-trastuzumab arms, and estimates of OS at 3 years were 96.3% and 89.7%, respectively. The HERA trial compared 1 or 2 years of trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) treatment with observation, in patients with HER2+ breast cancer who had received locoregional therapy and neoadjuvant or adjuvant chemotherapy (56). Results for the observation group of patients and the 1-year trastuzumab treatment group of patients were reported at a median follow-up of 1 year (57). Kaplan-Meier curves showed an estimated 2-year DFS of 85.8% in the trastuzumab arm vs 77.4% in the observation arm (P<0.0001), and a 2-year time to disease recurrence of 90.6% *vs* 82.8% (P<0.0001). However, overall survival was not significantly different between the treatment groups. In a trial with a similar design (PACS-04), patients with node-positive breast cancer were randomly assigned to receive adjuvant therapy as follows: 6 cycles of FEC (5-fluorouracil 500 mg/m^2; epirubicin 100 mg/m^2; cyclophosphamide 500 mg/m^2 every 3 weeks) or 6 cycles of ED (epirubicin 75 mg/m^2; docetaxel 75 mg/m^2 every 3 weeks), followed by radiotherapy (58). When HER2 status of the tumors became available, patients with HER2+ tumors were randomly assigned to receive 1 year of trastuzumab therapy (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks) or observation only. At 4 years, DFS was not significantly different between the trastuzumab and observation treatment arms.

Overall, these studies demonstrate a consistent efficacy of trastuzumab in the adjuvant setting, especially when it is administered concurrently with chemotherapy. The next-generation trial, ALTTO, will assess the relative efficacies of trastuzumab, lapatinib, and trastuzumab plus lapatinib in the adjuvant setting. This study consists of 4 treatment arms: paclitaxel plus trastuzumab; paclitaxel plus lapatinib; paclitaxel plus trastuzumab for 12 weeks followed by a 6-weeks washout period, followed by lapatinib for 34 weeks; and paclitaxel plus lapatinib plus trastuzumab. All study participants must have received at least 4 cycles of an approved anthracycline-containing (neo-)adjuvant chemotherapy regimen. This study is currently recruiting patients.

5.HER2-TARGETED AGENTS IN THE NEOADJUVANT SETTING

The use of HER2-targeted agents as part of a neoadjuvant regimen is less well-studied; however, encouraging data for HER2-targeted therapies have emerged in this treatment setting.

A trial investigating the efficacy of neoadjuvant therapy with paclitaxel (225 mg/m^2, 24 hours continuous infusion, every 3 weeks for 4 cycles) followed by FEC (5-fluorouracil 500 mg/m^2 on days 1 and 4, epirubicin 75 mg/m^2 on day 1, cyclophosphamide 500 mg/m^2 on day 1) randomly assigned patients to receive trastuzumab (a loading dose of 4 mg/kg followed by weekly doses of 2 mg/kg, for a total of 24 doses of trastuzumab) or no trastuzumab (59). Pathologic complete response (pCR), and a generally good PFS and OS, was seen in 15 of 23 (65.2%) patients in the trastuzumab treatment arm, and in 5 of 19 (26.3%) patients in the no-trastuzumab arm. An updated analysis, which included data on additional patients, showed that 12 of 22 (54.5%) of the additional patients, treated with chemotherapy plus trastuzumab, achieved a pCR (60).

The NOAH trial assessed the efficacy of chemotherapy with or without trastuzumab in the neoadjuvant setting. Patients who had HER2+ disease were randomized to 1 of 2 treatment arms: doxorubicin (60 mg/m^2) and paclitaxel (150 mg/m^2) every 3 weeks, for 3 cycles, followed by 4 cycles of paclitaxel (175 mg/m^2 every 3 weeks) and 3 cycles of CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2 every 4 weeks, on days 1 and 8), followed by surgery and radiotherapy; or the same chemotherapy regimen with trastuzumab (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks) for 1 year before surgery, and following surgery (61). A pCR was achieved in 43% of patients in the trastuzumab arm vs 23% of those in the no-trastuzumab arm (P=0.002). Patients in the trastuzumab arm also benefitted in terms of event-free survival (HR 0.56) and OS (HR 0.65).

The Neo-ALTTO study has been designed to assess the efficacies of lapatinib and trastuzumab in the neoadjuvant setting. In this study, patients will be randomized in three treatment arms: lapatinib followed by lapatinib plus paclitaxel; trastuzumab followed by trastuzumab plus paclitaxel; lapatinib plus trastuzumab followed by lapatinib plus trastuzumab plus paclitaxel. This study is currently enrolling patients. The CALGB 40601 study also will assess the activity of trastuzumab and lapatinib in the neoadjuvant setting and will assign patients to 3 treatment arms: trastuzumab plus lapatinib plus paclitaxel; trastuzumab plus paclitaxel; or lapatinib plus paclitaxel. This study is currently recruiting participants.

A summary of the characteristics of the clinical trials evaluating the HER2-targeted agents in the neoadjuvant setting is presented in Table 2.

6.HER2-TARGETED AGENTS: CARDIOTOXICITY

A key issue for HER2-targeted agents is the onset of cardiotoxicity. It was noted in the pivotal phase III trial with trastuzumab and in subsequent trials that a significant number of patients who received trastuzumab

Table 2. Phase III clinical trials investigating HER2-targeted agents in the neoadjuvant setting

Trial	Population	Trial design	End points
MDACC ID99-146 (clinicaltrials.gov identifier: NCT00038402)	HER2+ LABC	ARM A: PTX q3w 24-h c.i. x4 → FEC x4 ARM B: CT (PTX q3w 24-h c.i. x4 → FEC x4) + T qw x24 wks	Primary: pCR
NOAH (ISRCTN86043495)	HER2+ LABC	ARM A: AP x3 → PTX q3w x4 → $FEC_{1,8}$ x3 ARM B: CT like arm A + T q3w x10 (after surgery, RT and continue T up to complete 1 year of treatment; HR if ER+ and or PR+ BC)	Primary: EFS Secondary: pCR, total pCR, ORR, cardiac safety, and OS in all the three groups of patients, and EFS in patients with HER2- LABC
Neo-ALTTO (clinicaltrials.gov identifier: NCT00553358)	HER2+ LABC	ARM A: L_1 x6 wks → L_1+ PTX qw x12 ARM B: T qw x6 → T + PTX qw x12 → Surgery → T qw + $FEC_{1,8}$ x3 ARM C: L_2 + T qw x6 → L_3 + T + PTX qw x12 → Surgery → L_2 + T qw + $FEC_{1,8}$ x3	Primary: pCR Secondary: safety & tolerability, ORR, rate of N- at surgery, rate of conservative surgery, DFS, OS, PET/CT imaging, biomarkers, CTC
CALGB 40601 (clinicaltrials.gov identifier: NCT00770809)	HER2+ LABC	ARM A: L_1 + T + PTX qw x16 wks ARM B: T + PTX qw x16 wks ARM C: L_1 + PTX qw x16 wks	Primary: pCR in the breast Secondary: pCR in the breast and axilla, clinical response at completion of NACT, radiographic response at completion of NACT, OS, invasive RFS, time-to-first failure, toxicity

Abbreviations: LABC, locally-advanced breast cancer; q3w, every 3 weeks; 24-h c.i., 24-hours continuous infusion; qw, weekly; wks, weeks; pCR, pathologic complete response; CT, chemotherapy; RT, radiation therapy; HT, hormonal therapy; ER+, estrogen receptor-positive; PR+, progesterone receptor-positive; BC, breast cancer; EFS, event-free survival; ORR, overall response rate; OS, overall survival; N-, node negative; DFS, disease-free survival; PET/CT, positron emission tomography/computed tomography; CTC, circulating tumor cells; NACT, neoadjuvant chemotherapy; RFS, relapse-free survival; Chemotherapy Schedules: PTX q3w 24-h c.i., paclitaxel 225 mg/m^2 24-hours continuous infusion every 3 weeks; $F_{1,4}EC$, 5-fluorouracil 500 mg/m^2 on days 1 and 4 + epirubicin 75 mg/m^2 + ciclophosphamide 500 mg/m^2 on day 1 every 3 weeks; AP, doxorubicin 60 mg/m^2 + paclitaxel 150 mg/m^2 every 3 weeks; PTX q3w, paclitaxel 175 mg/m^2 every 3 weeks; $FEC_{1,8}$, 5-fluorouracil 600 mg/m^2 + methotrexate 40 mg/m^2 + ciclophosphamide 600 mg/m^2 on days 1 and 8 every 4 weeks; T q3w, trastuzumab 8 mg/kg loadiong dose then 6 mg/kg every 3 weeks; L_1, lapatinib 1500 mg daily; PTX qw, paclitaxel 80 mg/m^2

developed cardiac dysfunction, particularly when it was given concurrently with anthracyclines (62). Subsequent studies have shown that this cardiotoxicity is generally reversible and that trastuzumab may be reintroduced in some patients after resolution of the trastuzumab-induced cardiac dysfunction. An FDA review evidenced the onset of cardiotoxicity in patients enrolled in 4 adjuvant breast cancer trials (NCCTG N9831, NSABP B-31, HERA, and BCIRG 006) concluding that there is a 4- to 6-fold increase in symptomatic myocardial dysfunction in patients who were treated with trastuzumab (63). It is recommended that patients who are candidates for trastuzumab therapy undergo a baseline assessment of risk for cardiac dysfunction, including a patient history, physical exam, and left ventricular ejection fraction (LVEF) assessment by multiple gated acquisition scan (MUGA) or echocardiogram. LVEF monitoring should be continued throughout the period of treatment with trastuzumab; although there is no evidence that such monitoring can prevent the development of symptomatic cardiac dysfunction. It is recommended that trastuzumab be withheld from patients with a ≥16% absolute decrease in LVEF from pretreatment values, and from patients with an LVEF value below institutional limits of normal and a ≥10% absolute decrease in LVEF from pretreatment values.

Cardiac safety has also been studied in patients who have been treated with lapatinib. A pooled analysis of data from 3689 patients in 44 clinical trials demonstrated that cardiac events occurred in a small percentage of patients (asymptomatic events in 1.4% of patients, symptomatic events in 0.2% of patients) (63). LVEF decreases were seen in a significant proportion of patients but, as seen with patients treated with trastuzumab, were often reversible. As with trastuzumab, LVEF assessment before beginning treatment with lapatinib, and throughout the treatment period, is recommended.

7. NEW AGENTS AND NEW COMBINATIONS TO TARGET HER2

A number of clinical trials are under investigation to assess the efficacy of new HER2-targeted agents, also in combination regiments with lapatinib or trastuzumab . These agents include antibodies and specific protein inhibitors. Trastuzumab-DM1 (T-DM1), an antibody-drug conjugate that combines trastuzumab with DM1, a potent anti-microtubule agent, has shown activity in patients with HER2-overexpressing advanced or metastatic breast cancer in a number of studies (65, 66). Other antibodies in development include pertuzumab, a humanized monoclonal antibody that binds to the dimerization domain of HER2, which has shown promising activity in combination with trastuzumab or in monotherapy for patients whose breast cancer has progressed to therapy with trastuzumab (67, 68) or with the anti-vascular endothelial growth factor (VEGF) antibody, bevacizumab (69). Neratinib, an irreversible pan-HER receptor tyrosine kinase inhibitor, which has demonstrated activity in combination with trastuzumab or in monotherapy. (70). Pazopanib, an inhibitor of angiogenesis that targets VEGF receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and c-Kit, is being studied in combination with lapatinib (71), while tanespimycin, a heat shock protein-90 inhibitor, has shown clinical activity in combination with trastuzumab in

patients whose cancer has progressed to therapy with trastuzumab (72). RAD001 (everolimus), a mammalian target of rapamycin (mTOR) inhibitor, has been studied in combination with trastuzumab and other agents in patients with HER2+ metastatic breast cancer (73, 74).

8. CONCLUSIONS

Current evidence suggests that the treatment with drugs blocking the EGFR pathway is an effective treatment strategy, which improves the clinical outcome of patients with metastatic as well as early breast cancer. Trastuzumab and lapatinib, which are able, with different mechanism of action, to interphere with intracellular signaling leaving from EGFR receptors, are the first two drugs introduced in clinical practice belonging to this family, but a number of new molecules, as TDM1, Neratinib, Pazopanib, are already on study and will soon enrich our therapeutic armamentarium warranting further improvement in the treatment of this disease.

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Key Words: Breast Cancer, Her2, Egfr, Tirosine-Kynase, Trastuzumab, Lapatinib, Targeted Therapy, Review

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