Lapatinib in the management of breast cancer

Lapatinib is licensed for use in combination with capecitabine for the treatment of patients with progressive advanced breast cancer whose tumors overexpress the human epidermal growth factor receptor 2 (HER2/erbB2/HER2-neu), following therapy with an anthracycline, a taxane and trastuzumab. Lapatinib targets both the epidermal growth factor receptor (EGFR/HER1/erbB1) and HER2, and represents one of the most promising of a number of pharmacological attempts to bypass resistance mechanisms to trastuzumab. Further studies are being conducted to examine the potential role of lapatinib in the management of breast cancer in both the early and advanced setting. This article evaluates the pharmacology, tolerability and clinical efficacy of lapatinib. The future roles of lapatinib in the treatment of breast cancer are also discussed.

KEYWORDS: antineoplastic agents ▪ breast neoplasms ▪ epidermal growth factor receptor ▪ female ▪ HER2 receptor ▪ humans ▪ lapatinib ▪ protein kinase inhibitors

Peter S Hall[1†], Jaishree Bhosle[2] & David A Cameron[3]

[†]Author for correspondence:
[1]Clinical Research Fellow, University of Leeds, Charles Thackrah Building, Room 1.40, 101 Clarendon Road, Woodhouse, Leeds, LS2 9LJ, UK
Tel.: +44 113 343 0814
Fax: +44 113 343 2242
p.s.hall@leeds.ac.uk
[2]UCL Cancer Institute, UK
[3]Director, National Cancer Research Network, University of Leeds, UK

Approximately a fifth of women with breast cancer have tumors that overexpress human epidermal growth factor receptor 2 (HER2) [1]. Their cancer is characterized by aggressive features and a worse prognosis [2,3]. Lapatinib in combination with capecitabine is approved for the treatment of patients with advanced or metastatic breast cancer (MBC) whose tumors overexpress HER2. Specifically, patients should have progressive disease following prior therapy, which must include an anthracycline, a taxane and therapy with trastuzumab in the metastatic setting.

Targeting HER2

The *HER2*/*neu* oncogene was discovered in the 1980s, and is a member of the *erbB* oncogene family. It is related to, but distinct from, epidermal growth factor receptor (EGFR), and shares a role in the regulation of cell proliferation. Trastuzumab has dramatically improved outcomes for patients with HER2-positive breast cancer; however, data from seminal clinical trials tells us that half of all patients still have non-responding tumors, and disease progression occurs within 1 year in the majority of cases [4].

Trastuzumab resistance & the role of lapatinib

Lapatinib targets both EGFR and HER2, and represents a promising attempt to bypass resistance to trastuzumab. The mechanisms through which resistance develops are far from being well defined, but include increased cell signaling (e.g., phosphatase and tensin homlog gene [*PTEN*] loss, increased AKT activity), alternative cell signaling mediated by EGFR family pathways (e.g., transforming growth factor α overexpression or neuregulin overexpression) or alternative pathways (e.g., vascular endothelial growth factor [VEGF] or insulin-like growth factor-1 [IGFR-1] overexpression) [5]. In particular, the relevance of HER2 p95 needs to be considered; HER2 p95 is a truncated membrane-associated fragment of HER2 that has lost its extracellular domain (ECD) through proteolytic cleavage; *in vitro* studies suggest that p95 has a more active tyrosine kinase [6]. In addition, due to the lack of an ECD, antibodies like trastuzumab are not able to act, and lapatinib offers the potential to overcome this by targeting the intracellular kinase part of the receptor. Further studies are being conducted to examine the potential role of lapatinib in the management of breast cancer in the neoadjuvant, adjuvant and metastatic settings, both as a single agent and in combination with other therapies. Despite the fact that lapatinib inhibits both EGFR and HER2, EGFR expression has been shown not to predict response to lapatinib either *in vitro* [7] or in the clinical setting [8]. For this reason clinical trials of lapatinib are aimed at patients with HER2 overexpressing tumors, which correlate with response to lapatinib [8].

Lapatinib chemistry

Lapatinib ditosylate monohydrate is an oral, 4-anilinoquinazoline-derived, reversible kinase inhibitor with a molecular weight of 943.5

part of future medicine fsg

(FIGURE 1) [101]. It inhibits receptor phosphorylation and prevents the resulting activation of downstream signaling pathways [9,10].

Pharmacodynamics & metabolism

Lapatinib was designed to specifically target the ATP binding sites of EGFR and HER2, following preclinical studies showing that dual EGFR and HER2 inhibition produced synergistic inhibition of cell growth [11]. These receptors are part of the HER family, which has two other members: HER3 and HER4. All receptors span the cell membrane with extracellular, membrane spanning and cytoplasmic domains [12]. The intracellular domains of the HER family are highly conserved and all, except HER3, contain an intrinsic tyrosine kinase. In contrast, the ECDs differ between each receptor and have differing affinities for activating ligands, except for HER2, which permanently maintains an active conformation and has no ligand [12]. Upon ligand binding, HER-1, -3 and -4 undergo a conformational change to reveal a dimerization arm through which they interact with other receptors to form homo- and hetero-dimers [12]. In addition to other members of the HER family, HER1 is also able to dimerize with platelet-derived growth factor receptor (PDGFR) and IGFR-1 [13]. Dimerization allows the cross-phosphorylation of the intracellular carboxyl-tails of each receptor, which attracts adapter proteins and activates a number of downstream signaling pathways, including the Ras–Raf–MAPK and phosphoinositol-3-kinase (PI3K)/AKT pathways, as well as others that control cell proliferation, migration, differentiation and apoptosis [12,13]. In addition, HER proteins have been shown to translocate from the cell membrane to the nucleus, where their role is unclear, but they are thought to be able to act as transcription factors and promote DNA repair [14–16].

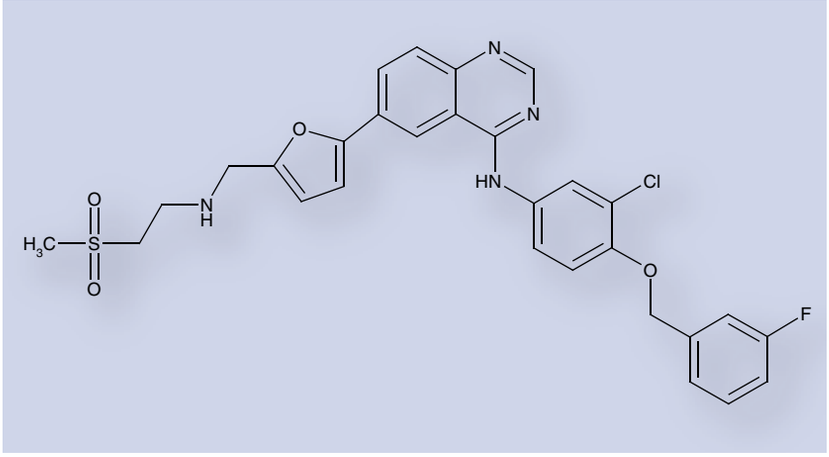

Figure 1. Lapatinib ditosylate monohydrate.

Preclinical studies have confirmed that lapatinib is able to inhibit key cell signaling pathways including the Ras–Raf–MAPK and PI3K/AKT pathways. In addition, the drug is able to inhibit cell proliferation and induce apoptosis in a variety of cell lines [17,18]. Inhibition of phosphorylation of EGFR and HER2 has also been demonstrated during treatment with lapatinib in a number of epithelial tumors in the clinical setting [19].

Pharmacokinetics

A number of Phase I studies have been conducted and reported a range of pharmacokinetic data, which are discussed later.

Lapatinib is delivered in tablet form, with each 250 mg tablet containing the equivalent of 405 mg of lapatinib ditosylate monohydrate [101]; it is poorly soluble in water, but tablets can be dispersed in water to aid administration. Absorption of the drug varies with diet (see below) and is delayed by around 30 min, with peak plasma concentration occurring 4 h after ingestion [10,101]. Lapatinib has a high volume of distribution (>2200 l) and is 99% bound to plasma proteins [10,101]. The dosing of lapatinib described in the package insert is based on that used in the pivotal Phase III registration trial. It recommends once-daily dosing, on an empty stomach 1 h before or after food. Daily dosing achieves a steady state within 6–7 days, with a half-life of 24 h. Dosing for lapatinib used within its licensed indication in combination with capecitabine was defined by the Phase I EGF10005 trial. The optimal tolerated dose was lapatinib 1250 mg once-daily plus capecitabine 1000 mg/m^2 twice-daily [20].

There remains debate concerning the optimum dosing schedule when used as monotherapy. A randomized, controlled trial recently reported a comparison of lapatinib 1500 mg once-daily or 500 mg twice-daily as first-line therapy in metastatic breast cancer patients [21]. There were no differences in response rate or progression-free survival between the two arms. No pharmacokinetic or pharmacodynamic data has been reported for monotherapy, leaving us no further forward in selecting the optimal schedule. There is evidence that absorption of lapatinib can increase up to fourfold if taken with a high-fat meal [10,101], and that toxicity can be reduced by administration with a meal [22]. This conflicts with the current recommendation to take

lapatinib while fasting, but does have the potential to reduce the tablet burden for patients and the economic burden for healthcare providers [23].

Elimination occurs via the liver, with 27% of oral dose recovered in feces, and less than 2% in the urine [9,10,101]. Hepatic metabolism is via the cytochrome P450 enzymes CYP3A4, 3A5, 2C8 and 2C19, and a 63% increase in AUC is seen in patients with severe hepatic impairment as defined by a Child–Pugh class C [10,101]. Dose reductions are recommended in patients taking CYP3A4 inhibitors (e.g., ketoconazole or clarithromycin), with increases suggested in patients taking CYP3A4 inducers (e.g., dexamethasone, carbamazepine and St John's wort) [10,101]. Lapatinib is both a substrate for, and an inhibitor of, the transporters P-glycoprotein and breast cancer resistance protein [101]. For this reason caution is advised when using lapatinib in conjunction with other P-glycoprotein substrates, although specific interactions have only been studied in combination with the chemotherapy agents detailed below.

Early clinical trials of lapatinib as a single agent

The initial Phase I clinical trials with lapatinib were conducted as dose-finding studies assessing both tolerability and toxicities. Further Phase I studies have been conducted in cancer patients with a view to examine the combination of lapatinib with anticancer therapies. Data specific to breast cancer is discussed separately.

Much of the initial toxicity and pharmacokinetic data was gained from a study conducted in 33 healthy volunteers [24]. The initial phase of this study was conducted in two groups of eight volunteers in an ascending dose, double-blind, randomized, placebo-controlled, four-way crossover trial. Within this group each volunteer received three doses of lapatinib and one dose of placebo, at 14-day intervals [24]. The first group of eight received doses of 10, 50 and 175 mg; the second group 25, 100 and 250 mg. The second phase of this study involved the assessment of multiple dosing in an ascending-dose, double-blind, randomized, placebo-controlled, staggered parallel design trial [24]. A total of 27 volunteers were enrolled in this part of the study, split into three groups of nine, with six volunteers receiving the drug and three placebo, taken once-daily for 8 consecutive days. The first group received 25 mg, the second 100 mg and the third 175 mg. Single doses of 250 mg and multiple doses of 175 mg were well-tolerated and no grade 3 or 4 toxicities were reported, and the most common side-effect was headache [24].

In cancer patients, lapatinib has been studied in 67 heavily pretreated patients with metastatic cancer [25]. Eligibility for the study included the requirement for expression of EGFR and/or overexpression of HER2 ($2/3^+$ immunohistochemistry [IHC] or fluorescence *in situ* hybridization [FISH] demonstrated gene amplification). This study was a randomized parallel-group, repeated dose-ranging study. Participants were randomized to one out of five dose groups; 500, 650, 900, 1200 and 1600 mg for 21 days. A protocol amendment added two further groups at 1000 and 2000 mg, but the latter group was never recruited. A total of 66% of patients experienced drug-related adverse events, with the most frequent reported as diarrhea (42%), rash (31%), nausea (13%) and fatigue (10%). Most were recorded at grade 1 or 2, with no grade 4 toxicities reported. Grade 3 toxicities included diarrhea, gastroesophageal reflux and skin rash. There were no reports of interstitial pneumonitis or drug-related reduction in left ventricular ejection fraction (LVEF). Grade 3 diarrhea was related to drug dose, but not plasma concentration. Four (7%) of the 59 evaluable participants reported a partial response, all of whom had breast cancer overexpressing HER2, and three with co-expressed EGFR.

Early clinical trials of lapatinib in combination with chemotherapy

Six Phase I studies have been reported examining the combination of lapatinib with chemotherapy regimens in patients with advanced cancer. In one study of 45 patients, the only complete response (CR) was seen in a patient with inflammatory breast cancer (IBC) (discussed later). Three confirmed partial responses (PRs) were seen in patients with breast, gastric and head and neck cancer [20].

Lapatinib has been studied in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV) (FOLOFOX regimen) [26]. The dose of 1500 mg/day in combination with standard FOLFOX was defined as the optimally tolerated regime, and this was used in 21 patients enrolled in the pharmacokinetic study. The most common adverse advents were nausea (86%), diarrhea (85%), vomiting (65%), fatigue (53%), neuropathy (53%) and mucositis (50%). Confirmed PR were reported in two patients, one with colorectal cancer and the other with cholangiocarcinoma.

Lapatinib in combination with 5-FU, LV and irinotecan (FOLFIRI) has been found to increase the AUC of SN-38, the active metabolite of irinotecan, by 41% [27]. In this study conducted in

12 patients, the optimally tolerated regimen of FOLFIRI was determined as 60% of standard dose in combination with lapatinib 1250 mg/day. Dose-limiting toxicities were found to be grade 3 diarrhea and grade 4 neutropenia. Neutropenia has also been found to be a problem when lapatinib was combined with docetaxel. The optimally tolerated regimen of lapatinib in combination with docetaxel was reported as lapatinib 1250 mg daily, docetaxel 75 mg/m^2 three-weekly and pegfilgastrin in a study of 52 patients with advanced cancer [28]. Dose-limiting toxicities were reported as grade 4 neutropenia in one patient receiving lapatinib 1250 mg with docetaxel 60 mg/m^2 and 50 mg/m^2, leading to the addition of pegfilgastrin to the treatment regimen. Following this protocol amendment, the most frequent dose-limiting toxicities were diarrhea and skin rash. At the 9-week response assessment, two patients had confirmed PR (prostate and unknown primary cancers).

Lapatinib in combination with carboplatin has been studied in patients with platinum-sensitive ovarian cancer. Carboplatin at a dose of a three-weekly cycle at AUC6 and lapatinib 750 mg/day produced grade 3 neutropenia, leading to a reduction to AUC5 [29]. Despite this reduction, one out of the five patients enrolled developed grade 3 neutropenia, leading to excessive treatment delays.

The development of neutropenia when lapatinib is combined with carboplatin, FOLFIRI or docetaxel results in reduced doses of chemotherapy agents used in combinations compared with standard chemotherapy doses alone. This is despite the fact that pharmacokinetic data from these studies have shown no interaction between lapatinib and the chemotherapy agents involved, except for SN38. The reasons for the development of neutropenia in these circumstances requires further investigation.

A Phase II trial in the neoadjuvant/adjuvant setting demonstrated that the combination of paclitaxel, trastuzumab and lapatinib is not feasible with a lapatinib dose of 1000 mg daily. Over a third of patients thus far have required a lapatinib dose-reduction, and the study closed early with 95 patients accrued. Grade 3 diarrhea was excessive, despite supportive treatment [30].

Safety & toxicity of lapatinib

The larger studies in breast cancer have now accurately profiled the side effects of lapatinib. The most commonly reported adverse events are diarrhea and a dry acneiform skin rash, both of which can be reduced by strict adherence to toxicity management protocols [31]. For diarrhea, this involves the proactive use of antidiarrheals; skin rash is helped by generously applied emollients and, if required, antibiotics. The correlation between severity of rash and efficacy seen with other EGFR inhibitors has not been shown for lapatinib. Rare, but potentially life-threatening toxicities include interstitial pneumonitis and hepatic toxicity [31,32]. Used within its licensed indication, lapatinib adds relatively little to the toxicity of capecitabine alone. In the EGF100151 trial, discontinuation due to toxicity was equal between arms [33] (Table 1).

Cardiotoxicity & lapatinib

Cardiotoxicity manifesting as a symptomatic or asymptomatic reduction in LVEF is seen with other HER2 targeted agents. Concern therefore exists over the potential for cardiotoxicity with lapatinib, and there are reports of decreased LVEF. For this reason caution is advised with conditions that could impair the LVEF, and baseline measurements are recommended [34]. A theoretical concern also exits when combining lapatinib with capecitabine, which can cause cardiotoxicity in the form of coronary artery spasm or arrhythmias. In the EGF100151 study, there were no differences in median LVEF between treatment groups during the trial. There was one episode of Prinzmetal's angina in a patient who was subsequently found to have an asymptomatic drop in LVEF. There

Table 1. Summary of toxicity from the EGF100151 trial.

	Grade 1/2 adverse events (%)		Grade 3/4 adverse events (%)	
	L + *C*	*C*	*L* + *C*	*C*
Diarrhea	51	30	14	10
PPE	42	37	12	14
Nausea	42	42	2	2
Vomiting	24	20	2	2
Fatigue	21	21	3	4
Rash	27	13	2	1

C: Capecitabine; L: Lapatinib; PPE: Palmar–plantar erythrodysesthesia.

were four asymptomatic drops in LVEF in the combination arm, compared with two in the control arm.

A pooled analysis of 3689 patients who received lapatinib in 44 Phase I studies showed that a study-defined cardiac event only occurred in 1.6% of patients; decreases in LVEF being asymptomatic in 83% of cases, and 88% of patients for whom data existed regained partial or full cardiac function, regardless of continuation or discontinuation of lapatinib [35]. Data from Phase IIII and observational whole population studies will be essential in confirming cardiac safety in the treatment population.

Clinical trials of lapatinib in breast cancer

First-line treatment of metastatic breast cancer in combination with chemotherapy

The EGF300001 Phase III trial evaluated lapatinib or placebo in combination with paclitaxel as first-line therapy for MBC [36]. The target population of this trial was MBC patients with HER2-negative tumors (i.e., those not eligible to receive trastuzumab), but in fact, 87 patients with unknown HER2 status were recruited. Enrolled patients received paclitaxel 175 mg/m^2 every 3 weeks plus either lapatinib 1500 mg daily or placebo. In the intent-to-treat analysis of 579 patients, there was no overall significant difference in time-to-progression (TTP), the primary end point or overall survival (OS), suggesting a lack of efficacy in the HER2-negative MBC population.

After a preplanned central laboratory review of HER2 status, 86 of the 531 patients for whom tissue samples were available were found to be HER2-positive using FISH and/or IHC. Comparing the 49 patients in the paclitaxel–lapatinib arm with the 37 patients in the paclitaxel–placebo arm, median TTP was 36.4 versus 25.1 weeks, with a hazard ratio [HR] of 0.53 (95% CI: 0.31–0.89; p = 0.005). There was also a significant improvement in overall response rate and event-free survival, but the data is insufficiently mature to comment on overall survival to date.

As discussed previously, the EGF20009 trial examined the tolerability and activity of two lapatinib regimens, 1500 mg once-daily with 500 mg twice-daily [21]. This trial recruited women receiving first-line treatment for HER2 overexpressing MBC. Women who had received neoadjuvant or adjuvant therapy were permitted to enter the trial; however, no patient had received prior trastuzumab therapy. A total of 69 women were recruited in each arm, with 24% achieving a CR or PR overall (22% in the 1500 mg daily, and 26% in the 500 mg twice-daily arm, p = 0.691). Overall, 31% of women achieved a clinical benefit of CR, PR or stable disease (SD) lasting for at least 24 weeks, demonstrating a clinical activity in this setting.

Lapatinib after disease progression with trastuzumab therapy

Regulatory approval of lapatinib in the USA for use in combination with chemotherapy in advanced trastuzumab refractory breast cancer was granted on the basis of a planned interim analysis of the EGF100151 trial [37].

The clinical activity of lapatinib in combination with capecitabine was suggested in a Phase 1 trial [20]. This tested the combination in patients with previously treated, advanced solid malignancies, and confirmed its tolerability with no detectable pharmacokinetic interaction. Of the seven included patients with breast cancer, one each achieved a CR and a PR.

The EGF100151 trial recruited women with locally advanced or metastatic HER2-positive breast cancer that had progressed after treatment with regimens that included an anthracycline, a taxane and trastuzumab. They were randomly assigned in a 1:1 ratio to receive either combination therapy (lapatinib 1250 mg per day continuously plus capecitabine 1000 mg/m^2 twice daily on days 1–14 of a 21-day cycle) or monotherapy (capecitabine 1250 mg/m^2 twice daily on days 1–14 of a 21-day cycle).

HER2-positivity was defined as grade 3+ by IHC or grade 2+ by IHC plus positive gene amplification as tested by FISH based on local laboratory assessment. All patients had measurable disease by Response Evaluation Criteria In Solid Tumors (RECIST). The primary end point was TTP, as assessed by independent reviewers under blinded conditions. It was defined as time from randomization to tumor progression, or death related to breast cancer. The first preplanned interim analysis was performed after 121 disease progression events in 324 randomized patients, and demonstrated a significantly longer TTP for the combination arm with a hazard ratio (HR) of 0.49 (95% CI: 0.34–0.71; p < 0.001). Median TTP was 8.4 versus 4.4 months. In light of this and an acceptable safety profile, the Independent Drug Monitoring Committee (IDMC) recommended that the trial be closed and treatment crossover was permitted.

An updated analysis, including an additional 75 patients who had been recruited between the interim analysis and the stopping of the trial, has subsequently been published [33]. Taking this population of 399 randomized women with 184 TTP events, prolonged TTP was confirmed with a HR of 0.57 (95% CI: 0.43–0.77; $p < 0.001$). This corresponded to a difference in median TTP of 6.2 versus 4.3 months. OS did not demonstrate a statistically significant difference with a HR of 0.78 (95% CI: 0.55–1.12; $p = 0.177$) although, as the trial was ended early, it was insufficiently powered to detect an OS difference. In fact, any difference in OS is likely to have been attenuated by a treatment arm crossover effect. Response rates were 24% in the combination arm versus 14% in the monotherapy arm, corresponding to an odds ratio (OR) of 1.9 (95% CI: 1.1–3.4; $p = 0.017$).

Lapatinib was studied in the randomized, controlled trial EGF104900, alone or in combination with trastuzumab in patients with HER2-positive MBC who progressed on trastuzumab. A statistically significant increase in the primary end point progression-free survival (PFS) was seen in the combination arm. Grade 1/2 diarrhea was higher in the combination arm (53 vs 41%); acneiform rash was more common in the lapatinib-alone arm, possibly due to the higher lapatinib dose. Asymptomatic decline in LVEF (>20% and below the lower limit of normal) occurred in 5% of patients in the combination arm and 2% of patients in the lapatinib-alone arm. One death occurred due to cardiac toxicity in the combination arm [38].

Lapatinib in the management of inflammatory breast cancer

Inflammatory breast cancer generally accounts for between 1 and 6% of breast cancer cases worldwide and up to 20% of newly diagnosed breast cancer in North Africa [39–41]. The disease is characterized by an aggressive nature, a tendency to affect younger women, a high proportion of local and distant metastases present at diagnosis and lower overall survival [42]. There is an increased rate of HER2 positivity in IBC, with up to 60% being HER2-positive [43–46].

This led to optimism for the potential benefit of lapatinib in this disease. Supporting data first came from two Phase I trials (EGF10004 – lapatinib alone, and EGF10009 – lapatinib plus paclitaxel) in heavily pretreated unselected metastatic carcinomas. A total of five IBC patients were included in these trials, of which three had PR and one had a prolonged complete remission lasting 3 years. All four responding IBC tumors overexpressed HER-2 [25,47]. In response to this finding, a Phase II trial was initiated testing lapatinib 1500 mg daily in IBC patients whose tumors are refractory to, or relapsed following anthracycline therapy. This included two cohorts of IBC patients: 30 patients were assigned to cohort A if their tumor overexpressed HER2, regardless of EGFR expression; 15 patients were assigned to cohort B if their tumor expressed EGFR without HER2 overexpression. A total of 50% of patients had received prior trastuzumab. In cohort A, there were 13 PR and two CR (clinical response in the chest wall or skin or response by RECIST criteria = 50%) with a median PFS of 14 weeks (95% CI: 15–32 weeks; median follow-up time of 15.3 weeks); cohort B was closed early due to negligible responses (only one PR) [48]. In this trial, prior trastuzumab did not preclude response to lapatinib.

The preliminary results of a Phase II trial testing lapatinib as neoadjuvant therapy for newly diagnosed IBC were reported in 2006. Lapatinib 1500 mg daily was administered for 2 weeks, followed by 12 weeks treatment with lapatinib at the same dose plus paclitaxel 80 mg/m^2 weekly. A total of 30 patients had HER2-positive breast cancer and five were HER2-negative. Tumor biopsies were taken prior to treatment and after 2 weeks. A total of 95% (20 out of 21) of evaluable patients with HER2-positive tumors had a clinical response, with 12 patients responding in both RECIST measurable and chest wall sites of disease. In Cohort B, 100% (2 out of 2) of evaluable patients with HER2-negative tumors responded in RECIST and chest wall sites [49]. Mature data regarding the primary outcome of pathological complete response (pCR) is awaited, but this compares favorably with the current best treatment where combinations of an anthracycline and taxane produce responses of 70–80% [46].

Future research into lapatinib in IBC is underway by the European Organization for Research and Treatment of Cancer with a randomized Phase I/II trial (EORTC-10054) [102]. The Phase I component of this trial has already established that to deliver the standard dose of docetaxel 100 mg/m^2 three-weekly with lapatinib 1000 mg daily requires prophylactic growth colony stimulating factor [50]. The protocol will now move on to a second phase to study these drugs together following combination chemotherapy with fluorouracil, epirubicin and cyclophosphamide (FEC). The Phase II component will then establish pCR in

the neoadjuvant setting for locally advanced, inflammatory or large resectable breast cancer to one of three arms:

- Arm A: FEC then lapatinib and docetaxel
- Arm B: FEC then trastuzumab and docetaxel
- Arm C: FEC then lapatinib and trastuzumab and docetaxel

All patients will receive trastuzumab after surgery (FIGURE 2).

Lapatinib in the management of CNS metastases

Current evidence suggests that patients with HER2-positive MBC have a higher rate of CNS metastases by comparison of case series with historical controls [51,52]. When considering that up to a third of these breast cancer patients may develop CNS metastases during their illness, this represents a significant problem [53]. Retrospective evidence suggests that trastuzumab may impact on the survival of these patients [54], although this effect is thought to be limited due to an inability of trastuzumab to cross the blood–brain barrier [55]. In fact, the higher rate of CNS metastasis seen in HER2-positive breast cancer may be due to either a differential effect between the CNS and other metastatic disease combined with increased survival with systemic therapy, or simply a difference in the biology of this disease subtype [56,57].

Interestingly, in the updated analysis of the EGF100151 trial, symptomatic CNS metastases (at the time of first progression at any site) were seen in only four (2%) patients in the lapatinib plus capecitabine arm, versus 13 (6%) in the capecitabine-alone arm. Although not preplanned, this difference was statistically significant ($p = 0.045$) [33]. This effect is hypothesized to be due to the ability of the small-molecule lapatinib to cross the blood–brain barrier.

Dedicated trials have been undertaken to explore this further: a Phase II trial by Lin *et al.* recruited 39 patients with HER2-positive breast cancer and progressive brain metastases after prior trastuzumab treatment. A total of 37 patients had also developed tumor progression after cranial radiotherapy. Patients received lapatinib 750 mg twice-daily. One patient achieved a PR in the brain by RECIST (objective response rate 2.6%, 95% conditional CI: 0.21–26%). The study did not meet the predefined criteria for antitumor activity; however, seven (18%)

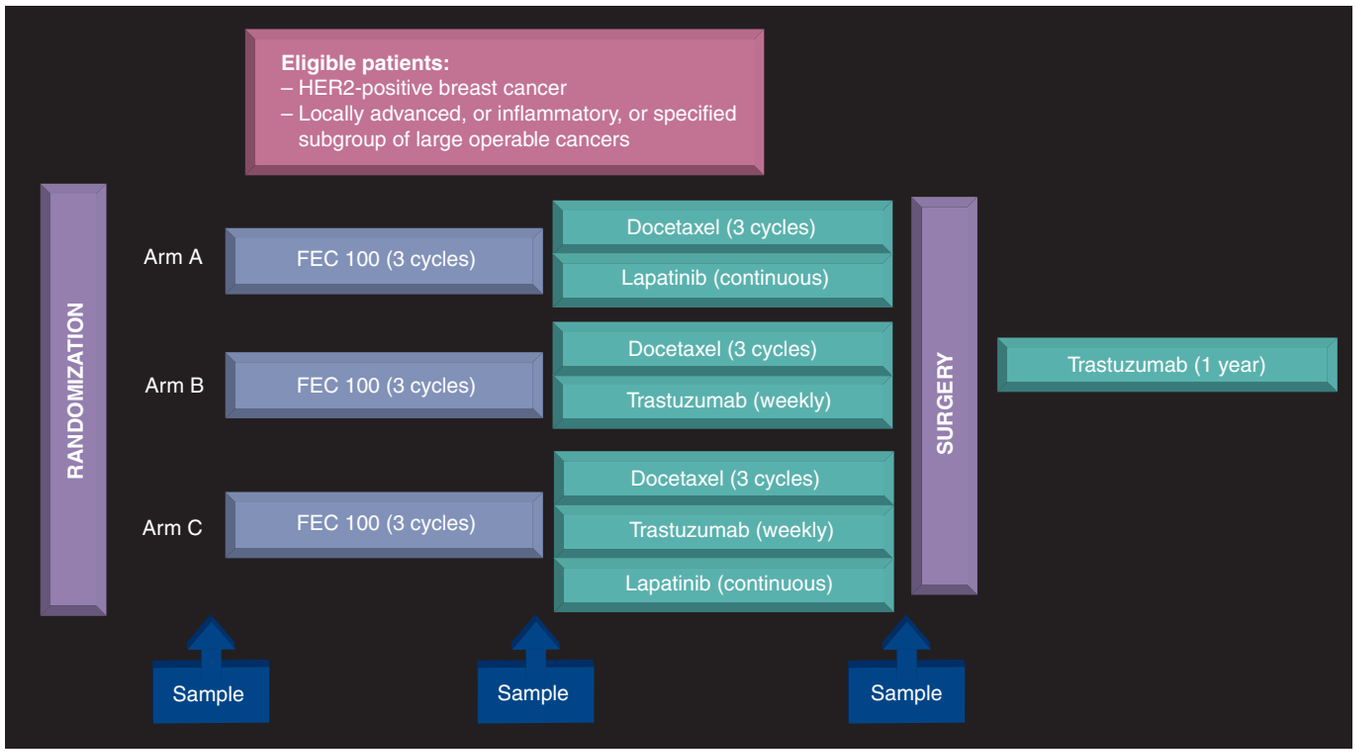

Figure 2. EORTC-10054 trial design – Phase II component. FEC 100 = 5-flurouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m² every 3 weeks. Docetaxel = 3-weekly dose per results of Phase I component. Lapatinib = daily oral dose per results of the Phase I component. Trastuzumab = 100 mg/m². Sample: core biopsy, serum sample, cardiac monitoring.
HER2: Human epidermal growth factor receptor 2.

patients were progression free in both CNS and non-CNS sites at 16 weeks. The median TTP was 3 months (95% CI: 2.3–3.7) [58]. Following on from these exploratory results, a larger Phase II trial (EGF105084) was initiated to study a similar patient population, but introduced new criteria to define response. This was defined as at least a 50% volumetric reduction of CNS lesions in the absence of new lesions, a need for increased dose of steroids, progressive neurological signs/symptoms or progressive extra-CNS disease. The 241 enrolled patients were heavily pretreated. By the defined criteria, a PR was reported in 15 (6%) patients, and 102 (42%) patients had SD of greater than 8 weeks. The median PFS for all patients was 3.7 months [59]. As an extension to this trial, in response to the EGF100151 trial, patients who experienced progressive disease on single-agent lapatinib were given the option of receiving lapatinib (1250 mg daily) plus capecitabine (2000 mg/m^2 daily on days 1–14 of a 21-day cycle). Preliminary results from 51 patients are available which, by the same response criteria definitions, show that 10 (20%) had a PR and 18 (35%) had SD at 8 weeks [60]. These findings, which are also exploratory, add to the suggestion from the EGF100151 trial that lapatinib in combination with capecitabine is an active combination in CNS metastases from HER2-positive breast cancer.

Although modest activity has been demonstrated in CNS metastases in patients with HER2-positive breast cancer, this has been shown in a heavily pretreated group and further research is worthwhile. Future research includes the Lapatinib and Temozolomide for the Treatment of Progressive Brain Disease in HER-2 Positive Breast Cancer (LAPTEM) Phase I trial, which is looking at lapatinib and temozolomide in combination for the treatment of progressive brain disease in HER2-positive breast cancer [103]. Another Phase III trial, which has recently completed recruitment, is testing lapatinib plus capecitabine versus trastuzumab plus capecitabine in HER2-positive metastatic breast cancer [104].

Lapatinib in combination with endocrine therapy

Interest in the combination of HER targeting drugs and endocrine therapy has arisen from *in vitro* data demonstrating crosstalk between the estrogen receptor (ER) and growth factors, which may contribute to resistance to endocrine therapy [61,62]. In addition, there is evidence that tamoxifen or estrogen deprivation can upregulate the HER2 receptor to produce HER2-dependent acquired resistance [63]. An optimally tolerated dose of lapatinib 1500 mg/day in combination with letrozole 2.5 mg was defined by a dose escalation study in 12 patients with advanced cancer [64]. This study went on to examine this regimen in a further 27 patients. Although they found a higher incidence of diarrhea and skin rash than that reported in single-agent lapatinib trials, the combination with letrozole was generally well-tolerated. A total of 18 (46%) patients in this study had breast cancer, and one with an ER/PR/HER2-positive tumor achieved a PR to therapy. This combination was subsequently assessed in the EGF30008 randomized, controlled trial comparing letrozole 2.5 mg with and without lapatinib 1500 mg daily in women with hormone-receptor-positive untreated metastatic breast cancer. Recently reported results demonstrate an improvement in the primary end point PFS in the HER2-positive subgroup of 219 patients with a median PFS of 3.0 months with letrozole alone versus 8.2 months with letrozole in combination with lapatinib (HR: 0.71; 95% CI: 0.53–0.96) [65].

Further studies examining the combination of lapatinib with tamoxifen in breast cancer are currently being undertaken. These have an additional challenge due to complex CYP3A4-dependent interactions between these two agents [66]. Lapatinib in combination with fulvestrant is also being tested.

Predicting response to lapatinib

Standardization of the definition of HER2-positivity is vital if the results of multiple clinical trials are to be applied in routine clinical practice. The gold standard for establishing HER2-positivity in clinical trials is prospective testing by a central laboratory, defining a positive test result as positive by FISH or score 3+ on a 0 to 3+ scale by IHC, with 3+ defined as uniform intense membrane staining of more than 30% of invasive tumor cells; a score of 2+ requiring confirmation by FISH [67]. These guidelines were developed from trials of trastuzumab in breast cancer and have been variably applied in trials in lapatinib to date, but must be whole-heartedly adopted for future research. Indeed, retrospective analyses of the central HER2 testing status in the pivotal EGF100151 and EGF300001 studies suggest that the same cut-off predicts for lapatinib benefit [8].

Initial eligibility for the EGF100151 trial relied on local confirmation of HER2 positivity by the above definition. Subsequent central

review in 241 (77%) patient tissue samples provided an opportunity to test the prognostic and predictive value of the different testing methods. This exploratory analysis suggested that HER2-positive status by FISH was a stronger predictor for benefit from the addition of lapatinib to capecitabine compared with HER2 positivity by IHC staining.

Much work remains to be carried out in the further characterization of biomarkers for predicting benefits from lapatinib therapy. High serum HER2 ECD levels have been associated with poor response to chemotherapy [68,69] and improved response to trastuzumab [32]. However, serum HER2 ECD did not predict benefit from lapatinib in the EGF100151 trial. The analysis also found no differential benefit in patients by tumor expression of EGFR [8]. In the Phase II trial in IBC outlined above, phosphorylated HER-3 and lack of p53 expression predicted response to lapatinib ($p < 0.05$), and tumors co-expressing pHER-2 and pHER-3 were more likely to respond to lapatinib (nine of 10 vs four of 14; $p = 0.0045$) [48].

Regulatory & economic considerations

Lapatinib was approved by the US FDA on March 13, 2007, and marketing authorization was granted in the EU on 10th June, 2008. It is currently licensed only in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2. Specifically, patients should have progressive disease following prior therapy, which must include anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting. The recommended dose for the licensed indication is 1250 mg (five tablets) daily as a single dose [70]. Lapatinib is manufactured by GlaxoSmithKline (London, UK), and it has Tyverb® as a brand name in most of Europe, and Tykerb® in the USA.

Fully published peer-reviewed cost–effectiveness models are scarce for lapatinib, but it is undoubtedly an area of research priority for many countries. Any independent modeling so far places the cost per quality-adjusted-life-year well above common approval thresholds for publically funded healthcare systems [71,72]. Economic evaluation of lapatinib used for its licensed indication depends largely on what is taken as the current standard-of-care comparator after progression of HER2-positive MBC after an anthracycline, a taxane and trastuzumab, and this is far from clear. The obvious analysis compares capecitabine alone with capecitabine plus lapatinib, but this may not accurately reflect clinical practice. Accepting the use of trastuzumab alone or with capecitabine beyond progression on trastuzumab or incorporating vinorelbine as a comparator in a proportion of patients may be more appropriate.

In the UK in 2008, the National Institute for Clinical Excellence (NICE) rejected the use of lapatinib in the NHS on cost–effectiveness grounds, assuming that the use of trastuzumab beyond progression was not a valid comparator, although it is widely used. However, in light of recent shifts in UK policy applied to the assessment of treatments at the end of life, the case for lapatinib has been reopened following appeal, and further guidance is due [105]. Elsewhere, such as in Germany and the USA, lapatinib is starting to be recommended for selected patients [106,107].

Various patient access schemes have been launched or proposed by the manufacturer pending further appraisal by healthcare decision makers.

Future perspective

Lapatinib as first-line treatment for HER2-postive MBC

EGF30001 demonstrates that the addition of lapatinib to paclitaxel in the first-line setting for the treatment of HER2-positive MBC produces benefits similar to those seen with the addition of trastuzumab to a taxane in the same setting (increase in TTP from approximately 7 months to around 8 months) [73–75]. Which of the two drugs is more beneficial can be answered by the EGF108919 trial, which involves a head-to-head comparison between the two drugs. The National Cancer Institute of Canada is conducting this trial, which involves randomization between lapatinib or trastuzumab in combination with either paclitaxel or docetaxel. The primary end point is PFS, and secondary end points include OS, incidence of CNS metastasis as first progression and time to CNS metastasis as first progression, clinical benefit rate and safety. Ongoing and planned trials testing lapatinib in breast cancer are summarized in TABLES 2 & 3.

Lapatinib therapy after progression on trastuzumab in MBC

From a broader perspective, the EGF100151 trial was the first randomized, controlled, prospective study demonstrating efficacy of continued anti-HER2 targeted therapy following progression on trastuzumab in advanced breast cancer. Apart from retrospective analyses, with their inherent weakness such as that conducted

Table 2. Selected ongoing or planned randomized trials in locally advanced or metastatic breast cancer.

Trial	Primary end point	Population	Treatment arms
EGF104900	PFS	Trastuzumab-refractory MBC	Trastuzumab + lapatinib vs lapatinib alone
EGF30001	TTP	First-line for patients with HER2-negative or untested MBC	Paclitaxel + lapatinib vs paclitaxel + placebo
EGF104535	CBR	First-line for HER2-positive MBC	Paclitaxel + lapatinib vs paclitaxel + placebo
EGF104383	TTP	First-line for HER2-positive MBC	Paclitaxel + trastuzumab + lapatinib vs paclitaxel + trastuzumab + placebo
EGF108919	PFS	Stage IV, HER2-positive	Taxane + lapatinib vs taxane + trastuzumab
CALGB 40302	PFS	Postmenopausal women with HR-positive, HER2-positive advanced breast cancer	Fulvestrant + lapatinib vs fulvestrant + placebo

CALGB: Cancer and Leukemia Group B; CBR: Clinical benefit rate; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; MBC: Metastatic breast cancer; PFS: Progression-free survival; TTP: Time to progression.

by Montemurri *et al.* [76], the only other robust evidence supporting this strategy is provided by the randomized trial GBG26/TBP, which set out to compare capecitabine with or without trastuzumab in patients who had progressed or relapsed after any prior trastuzumab treatment. This was closed early on the recommendation of the IDMC after recruiting 156 patients. The final analysis recently reported statistically significant advantages for the combination arm with increased response rates and mean TTP of 5.6 vs 8.2 months ($p = 0.034$) [77]. Although the effect size is similar to that seen with lapatinib in the EGF100151 trial, lower numbers and the consequent lower statistical certainty make it a weaker evidence base. Differences in the patient populations between these trials makes meta-analysis inappropriate. Controversy therefore remains regarding the optimum treatment in this refractory patient population after a taxane and an anthracycline, but taking these two trials together does strongly support the idea of continued anti-HER2 therapy after first progression on a trastuzumab-based regimen. Should we combine lapatinib or trastuzumab with capecitabine or an alternative chemotherapeutic agent such as vinorelbine? Answers may lie in novel combinations of therapies targeting resistance pathways, and investigation into this area is underway.

The combination of trastuzumab with escalating doses of lapatinib (750–1500 mg daily), has been investigated in patients with HER2-overexpressing breast cancer [78]. A total of 54 patients were enrolled, with 50 patients having received at least one prior trastuzumab-containing regime. Most patients reported at least one drug-related adverse advent. No grade 4 events were reported, the most common grade 3 toxicities were diarrhea, rash and fatigue. Pharmacokinetic studies were conducted in 27 patients. No significant differences were seen in the peak plasma concentration or AUC of either lapatinib or trastuzumab, in combination or as a single agent. Clinical response was assessed after 8 weeks. One CR, seven with PR and six with SD lasting longer than 6 months, were observed. All eight responders had received prior trastuzumab-containing chemotherapy [78].

Other novel combinations are being tested. The VEGF inhibitor bevacizumab has recently demonstrated clinical activity in a Phase II trial with an acceptable safety profile in combination with lapatinib in HER2-positive metastatic breast cancer after progression on standard therapies [79].

Lapatinib therapy in early breast cancer

The historical path of development for anticancer systemic treatments traditionally moves from the treatment of advanced disease in a palliative setting to use as curative therapy in early disease. Lapatinib is now being tested as adjuvant treatment after surgical treatment of early breast cancer. The challenge will be in finding a role complimentary to trastuzumab. Lapatinib may have a number of advantages, including its more convenient oral formulation,

Table 3. Ongoing or planned trials in early-stage breast cancer.

Trial	Primary end point	Population	Treatment arms
EGF105485 (TEACH)	DFS	HER2-positive, trastuzumab-naive patients who have completed adjuvant therapy	Lapatinib vs placebo
EGF105485 (ALTTO)	DFS	HER2-positive, adjuvant setting	Trastuzumab vs lapatinib vs sequential combination vs concurrent combination
EGF106903 (Neo-ALTTO)	pCR rate	HER2-positive, neo-adjuvant setting	Trastuzumab vs lapatinib vs concurrent combination
EORTC 10054	Phase I = MTD Phase II = pCR	HER2-positive, locally advanced, inflammatory, or large resectable breast cancer – after neoadjuvant FEC 100	Trastuzumab + docetaxel vs lapatinib + docetaxel vs lapatinib + trastuzumab + docetaxel
GeparQuinto (GBG)	pCR	HER2 positive breast cancer, neoadjuvant setting, concurrent with EC-T	EC-T + trastuzumab vs EC-T + lapatinib
CHERLOB	pCR	HER2 positive breast cancer, neoadjuvant setting, concurrent anthracycline then taxane	Trastuzumab vs lapatinib vs concurrent combination

ALTTO: Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimization; CHERLOB: Preoperative Chemotherapy plus Lapatinib or Trastuzumab or Both in HER2-Positive Operable Breast Cancer; DFS: Disease-free survival; EC-T: Epirubicin and cyclophosphamide followed by docetaxel; EORTC: European Organization for Research and Treatment of Cancer; FEC 100: 5-flurouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m² every 3 weeks; GBG: German Breast Group; HER2: Human epidermal growth factor receptor 2; MTD: Maximum tolerated dose; Neo-ALTTO: Neo-Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization; pCR: Pathological complete response; TEACH: Tykerb® Evaluation After Chemotherapy.

ability to cross the blood–brain barrier and its possibly lower cardiotoxicity; two global trials are under way.

The Tykerb Evaluation after Chemotherapy (TEACH; EGF105485) trial is a randomized, double-blind, placebo-controlled trial evaluating 1 year of lapatinib 1500 mg daily in patients previously treated with primary neoadjuvant or adjuvant chemotherapy. Eligibility defines patients with HER2-positive breast cancer who have no clinically or radiologically detectable cancer and have not received prior trastuzumab. The primary end point is disease-free survival and, with recruitment now complete, mature results are awaited [108].

The Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimization (ALTTO; EGF106708; BIG 2–06/N063D) trial offers a real opportunity to define best treatment strategies in women with HER2-positive early breast cancer. This large, multinational study commenced in February 2008 and aims to recruit 8000 patients from 1218 centers. There are two designs of the trial running concurrently; design one will enter patients following completion of all (neo)adjuvant chemotherapy, which must include at least four cycles of an anthracycline-based regimen, but no taxane. Design two will enroll patients who have also completed anthracyline-based chemotherapy, but in whom paclitaxel chemotherapy has been recommended. In this group patients will receive weekly paclitaxel concurrently with anti-HER2 therapy for the first 12 weeks. All patients are randomized to receive one of four possible combinations of anti-HER2 treatment: trastuzumab alone, lapatinib alone, lapatinib plus trastuzumab or trastuzumab for 12 weeks, 6 weeks 'washout' period and then lapatinib. In total, all participants will receive 52 weeks of therapy [109] (FIGURE 3).

The Neo-Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (NEO-ALTTO; BIG-1–06/EGF106903) is a trial looking at the use of lapatinib and/or

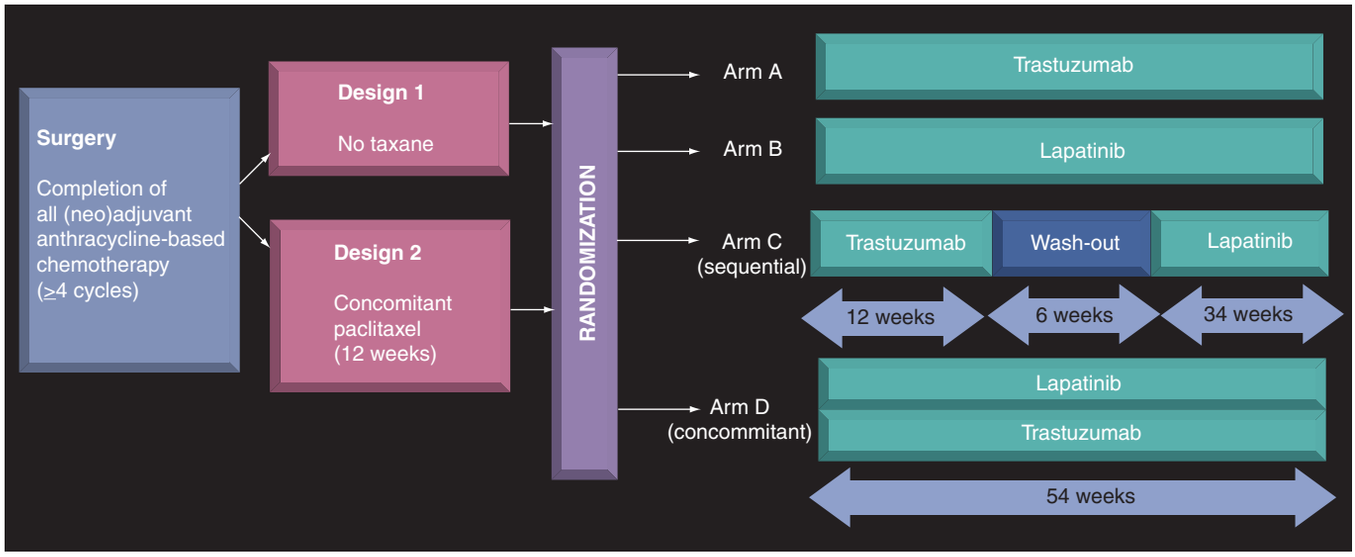

Figure 3. Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimization (ALTTO) trial design.

trastuzumab with neoadjuvant chemotherapy [110]. It is designed as a randomized, multicenter open-label trial of neoadjuvant paclitaxel plus lapatinib, trastuzumab or both in women with HER2-positive primary breast cancer. Imaging with positron emission tomography will take place at baseline and after 6 weeks of initial therapy. The recruitment target is 450 patients, with over 150 recruited since launch in December 2007 (FIGURE 4).

The Preoperative Chemotherapy plus Lapatinib or Trastuzumab or Both in HER2-Positive Operable Breast Cancer (CHERLOB) trial is a Phase IIb trial also looking at the neoadjuvant

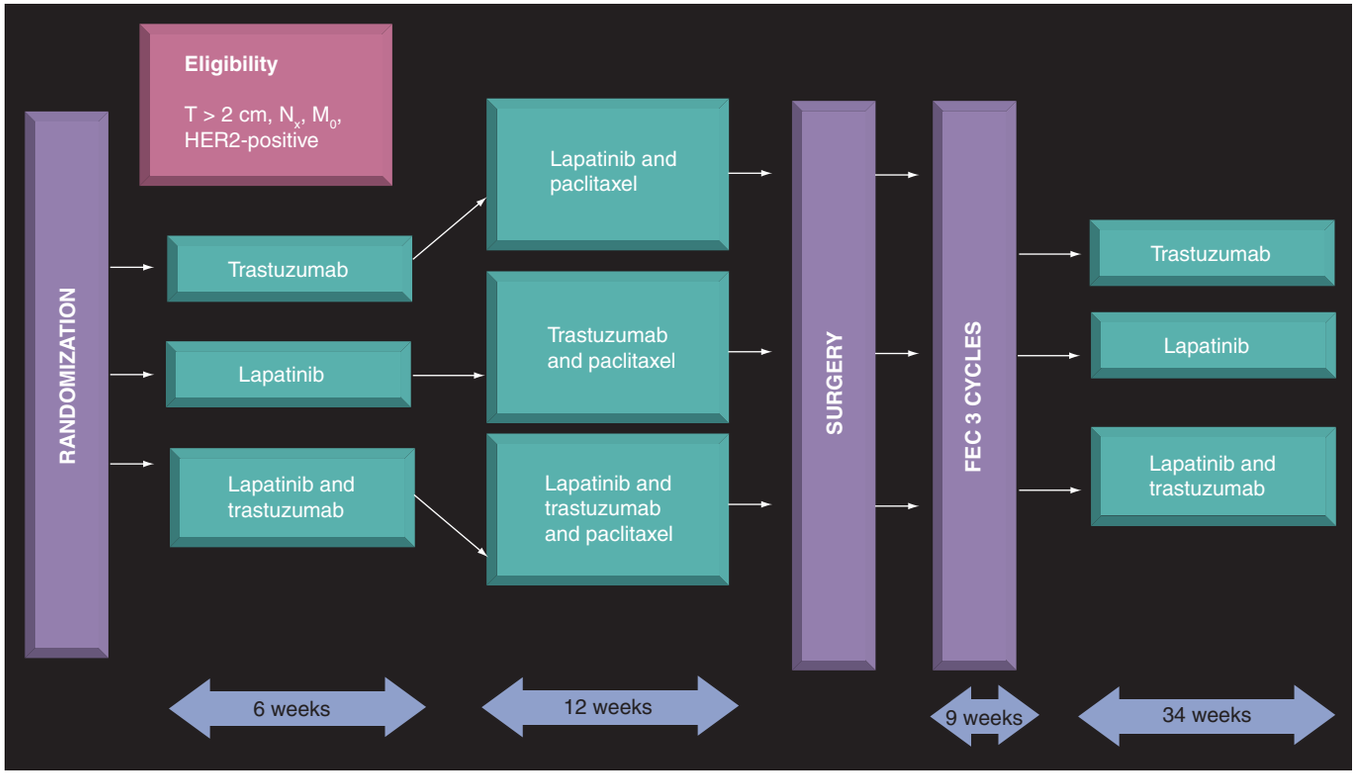

Figure 4. Neo-Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (NEO-ALTTO) trial design. Lapatinib 1500 mg/day. Paclitaxel 80 mg/m^2/week. Trastuzumab presurgery 2 mg/kg/week. Trastuzumab postsurgery 6 mg/kg/3-weekly.
FEC: 5-fluorouracil, epirubicin, cyclophosphamide; HER2: Human epidermal growth factor receptor 2.

setting. It combines lapatinib or trastuzumab or the combination with an anthracycline followed by a taxane. Early analysis of cardiac toxicity appears acceptable, and the trial continues to recruit [80].

Conclusion

Lapatinib in combination with capecitabine has established itself as a therapy for patients with HER2 overexpressing MBC following treatment with taxanes, anthracyclines and trastuzumab. Lapatinib has the advantage of being an oral formulation, although current advice is that it is taken on an empty stomach in view of alteration in absorption in the presence of high levels of fat. Lapatinib is mostly bound to plasma proteins, giving it a high volume of distribution. Metabolism is hepatic, and care should be taken in patients with liver impairment and when used in combination with other drugs that affect cytochrome P450 enzymes. The most common side effects are an acneiform skin rash and diarrhea which, in most cases, can be controlled. Rare, but potentially life-threatening toxicities include interstitial pneumonitis and hepatic toxicity. As with trastuzumab, the potential for decreases in LVEF should be considered, especially in those with impairment already. As clinical experience with lapatinib increases, the true cardiac risk should become apparent.

Further research into the roles of lapatinib in the treatment of IBC and in combination with endocrine therapy are underway. In addition, the roles of both lapatinib and trastuzumab in combination with chemotherapy in both metastatic and early breast cancer needs to be defined. There are a number of large Phase III trials underway to try and answer these questions. In addition, with increases in nonsurgical treatment options in HER2-overexpressing breast cancer, we need to attempt to accurately predict which treatment is best for an individual; not only to spare that individual from ineffective therapies, but also to ensure that healthcare budgets are spent effectively. Partnership and co-operation between the pharmaceutical industry, academic laboratory researchers and clinical trialists on a global scale is undoubtedly the key to success.

Financial & competing interests disclosure

Peter Hall is employed on a research grant to the University of Leeds provided by Roche. David Cameron has received honoraria from GSK and honoraria and research funding from Roche. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Mechanism of action

- Lapatinib competes with ATP to bind to ATP-binding site within the tyrosine kinase-containing intracellular domain of both epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2), inhibiting receptor phosphorylation.
- Lapatinib inhibits key cell signaling pathways including the Ras–Raf–MAPK and PI3K/AKT, through inhibition of EGFR and HER2 phosphorylation.

Pharmacokinetic properties

- Daily dosing achieves a steady state within 6–7 days, with a half-life of 24 h.
- 99% is bound to plasma proteins.
- Lapatinib is mainly hepatically metabolized via the cytochrome P450 enzymes (CYP3A4, 3A5, 2C8 and 2C19).

Dosage & administration

- Administered as 250 mg tablets taken on an empty stomach 1 h before or after food.
- Currently licensed dose is 1250 mg, taken once-daily in combination with capecitabine.

Safety & toxicity

- Diarrhea and a dry acneiform skin rash are common.
- Interstitial pneumonitis and hepatic toxicity are rare but life-threatening.
- Caution is advised in patients with decreased left ventricular ejection fraction.

Clinical efficacy

- Currently licensed for use in combination with capecitabine in patients with progressive metastatic breast cancer following treatment with anthracyclines, taxanes and trastuzumab (EGF100151 trial).
- Efficacy for HER2-positive inflammatory breast cancer and cerebral metastases from HER2-positive breast cancer (confirmatory research required).
- Efficacy as first-line treatment in combination with paclitaxel for HER2-positive metastatic breast cancer (confirmatory research required).

Bibliography

1 Owens MA, Horten BC, Da Silva MM: HER2 amplification ratios by fluorescence *in situ* hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. *Clin. Breast Cancer* 5, 63–69 (2004).

2 Slamon DJ, Godolphin W, Jones LA *et al.*: Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 244, 707–712 (1989).

3 Joensuu H, Isola J, Lundin M *et al.*: Amplification of erbB2 and erbB2 expression are superior to estrogen receptor status as risk factors for distant recurrence in pT1N0M0 breast cancer: a nationwide population-based study. *Clin. Cancer Res.* 9, 923–930 (2003).

4 Piccart-Gebhart MJ, Procter M, Leyland-Jones B *et al.*: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N. Engl. J. Med.* 353, 1659–1672 (2005).

5 Valabrega G, Montemurro F, Aglietta M: Trastuzumab: mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer. *Ann. Oncol.* 18, 977–984 (2007).

6 Segatto O, King CR, Pierce JH, Di Fiore PP, Aaronson SA: Different structural alterations upregulate *in vitro* tyrosine kinase activity and transforming potency of the erbB-2 gene. *Mol. Cell. Biol.* 8, 5570–5574 (1988).

7 Zhang D, Pal A, WG Bornmann *et al.*: Activity of lapatinib is independent of EGFR expression level in HER2-overexpressing breast cancer cells. *Mol. Cancer Ther.* 7, 1846–1850 (2008).

8 Press MF, Finn RS, D Cameron *et al.*: HER-2 gene amplification, HER-2 and epidermal growth factor receptor mRNA and protein expression, and lapatinib efficacy in women with metastatic breast cancer. *Clin. Cancer Res.* 14, 7861–7870 (2008).

9 Nelson MH, Dolder CR: A review of lapatinib ditosylate in the treatment of refractory or advanced breast cancer. *Ther. Clin. Risk Manag.* 3, 665–673 (2007).

10 Medina PJ, Goodin S: Lapatinib: a dual inhibitor of human epidermal growth factor receptor tyrosine kinases. *Clin. Ther.* 30, 1426–1447 (2008).

11 Burris HA 3rd: Dual kinase inhibition in the treatment of breast cancer: initial experience with the EGFR/ErbB-2 inhibitor lapatinib. *Oncologist* 9(Suppl. 3), 10–15 (2004).

12 Yarden Y, Sliwkowski MX: Untangling the ErbB signalling network. *Nat. Rev. Mol. Cell Biol.* 2, 127–137 (2001).

13 Bianco R, Gelardi T, Damiano V, Ciardiello F, Tortora G: Rational bases for the development of EGFR inhibitors for cancer treatment. *Int. J. Biochem. Cell Biol.* 39, 1416–1431 (2007).

14 Dittmann K, Mayer C, B Fehrenbacher *et al.*: Radiation-induced epidermal growth factor receptor nuclear import is linked to activation of DNA-dependent protein kinase. *J. Biol. Chem.* 280, 31182–31189 (2005).

15 Hsu SC, Hung MC: Characterization of a novel tripartite nuclear localization sequence in the EGFR family. *J. Biol. Chem.* 282, 10432–10440 (2007).

16 Lin SY, Makino K, Xia W *et al.*: Nuclear localization of EGF receptor and its potential new role as a transcription factor. *Nat. Cell Biol.* 3, 802–808 (2001).

17 Konecny GE, Pegram MD, Venkatesan N *et al.*: Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells. *Cancer Res.* 66, 1630–1639 (2006).

18 Kim JW, Kim HP, Im SA *et al.*: The growth inhibitory effect of lapatinib, a dual inhibitor of EGFR and HER2 tyrosine kinase, in gastric cancer cell lines. *Cancer Lett.* 272, 296–306 (2008).

19 Spector NL, Xia W, Burris H 3rd *et al.*: Study of the biologic effects of lapatinib, a reversible inhibitor of ErbB1 and ErbB2 tyrosine kinases, on tumor growth and survival pathways in patients with advanced malignancies. *J. Clin. Oncol.* 23, 2502–2512 (2005).

20 Chu QS, Schwartz G, de Bono J *et al.*: Phase I and pharmacokinetic study of lapatinib in combination with capecitabine in patients with advanced solid malignancies. *J. Clin. Oncol.* 25, 3753–3758 (2007).

21 Gomez HL, Doval DC, Chavez MA *et al.*: Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. *J. Clin. Oncol.* 26, 2999–3005 (2008).

22 Reddy N, Cohen R, Whtehead B: A Phase I, open-label, three-period, randomized crossover study to evaluate the effect of food on the pharmacokinetics of lapatinib in cancer patients. *Clin. Pharmacol. Ther.* 81(Suppl.), S16–S17 (2007).

23 Ciccarese M, Lorusso V: How should we prescribe lapatinib to our patients: once daily or twice daily, and at what dose? *J. Clin. Oncol.* 27, 314–315; author reply 315–317 (2009).

24 Bence AK, Anderson EB, Halepota MA *et al.*: Phase I pharmacokinetic studies evaluating single and multiple doses of oral GW572016, a dual EGFR-ErbB2 inhibitor, in healthy subjects. *Invest. New Drugs* 23, 39–49 (2005).

25 Burris HA 3rd, Hurwitz HI, Dees EC *et al.*: Phase i safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. *J. Clin. Oncol.* 23, 5305–5313 (2005).

26 Siegel-Lakhai WS, Beijnen JH, Vervenne WL *et al.*: Phase I pharmacokinetic study of the safety and tolerability of lapatinib (GW572016) in combination with oxaliplatin/fluorouracil/leucovorin (FOLFOX4) in patients with solid tumors. *Clin. Cancer Res.* 13, 4495–4502 (2007).

27 Midgley RS, Kerr DJ, Flaherty KT *et al.*: A Phase I and pharmacokinetic study of lapatinib in combination with infusional 5-fluorouracil, leucovorin and irinotecan. *Ann. Oncol.* 18, 2025–2029 (2007).

28 LoRusso PM, Jones SF, Koch KM *et al.*: Phase I and pharmacokinetic study of lapatinib and docetaxel in patients with advanced cancer. *J. Clin. Oncol.* 26, 3051–3056 (2008).

29 Kimball KJ, Numnum TM, Kirby TO *et al.*: A Phase I study of lapatinib in combination with carboplatin in women with platinum sensitive recurrent ovarian carcinoma. *Gynecol. Oncol.* 111, 95–101 (2008).

30 Dang CT, Lin NU, Lake D *et al.*: Preliminary safety results of dose-dense (dd) doxorubicin and cyclophosphamide (AC) followed by weekly paclitaxel (P) with trastuzumab (T) and lapatinib (L) in HER2 overexpressed/amplified breast cancer (BCA). *J. Clin. Oncol.* (Meeting Abstracts) 26 (2008) (Abstract 518).

31 Moy B, Goss PE: Lapatinib-associated toxicity and practical management recommendations. *Oncologist* 12, 756–765 (2007).

32 Esteva FJ, Valero V, Booser D *et al.*: Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer. *J. Clin. Oncol.* 20, 1800–1808 (2002).

33 Cameron D, Casey M, M Press *et al.*: A Phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res. Treat.* 112, 533–543 (2008).

34 Ewer M, Perez E, Baselga J: Cardiac safety guidelines for the adjuvant use of trastuzumab (Herceptin) in HER2-positive early breast cancer. *Breast* 16, S63 (2007).

35 Perez EA, Koehler M, Byrne J, Preston AJ, Rappold E, Ewer MS: Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin. Proc.* 83, 679–686 (2008).

36 Di Leo A, Gomez HL, Aziz Z *et al.*: Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. *J. Clin. Oncol.* 26, 5544–5552 (2008).

37 Geyer CE, Forster J, Lindquist D *et al.*: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N. Engl. J. Med.* 355, 2733–2743 (2006).

38 O'Shaughnessy J, Blackwell KL, Burstein H *et al.*: A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2$^+$ metastatic breast cancer progressing on trastuzumab therapy. *J. Clin. Oncol.* (Meeting Abstracts) 26, (2008) (Abstract 1015).

39 Anderson WF, Schairer C, Chen BE, Hance KW, Levine PH: Epidemiology of inflammatory breast cancer (IBC). *Breast Dis.* 22, 9–23 (2005).

40 Jaiyesimi IA, Buzdar AU, Hortobagyi G: Inflammatory breast cancer: a review. *J. Clin. Oncol.* 10, 1014–1024 (1992).

41 Chang S, Parker SL, Pham T, Buzdar AU, Hursting SD: Inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program of the National Cancer Institute, 1975–1992. *Cancer* 82, 2366–2372 (1998).

42 Walshe JM, Swain SM: Clinical aspects of inflammatory breast cancer. *Breast Dis.* 22, 35–44 (2005).

43 Parton M, Dowsett M, Ashley S, Hills M, Lowe F, Smith IE: High incidence of HER-2 positivity in inflammatory breast cancer. *Breast* 13, 97–103 (2004).

44 Sawaki M, Ito Y, Akiyama F *et al.*: High prevalence of HER-2/neu and p53 overexpression in inflammatory breast cancer. *Breast Cancer* 13, 172–178 (2006).

45 Dawood S, Broglio K, Gong Y *et al.*: Prognostic significance of HER-2 status in women with inflammatory breast cancer. *Cancer* 112, 1905–1911 (2008).

46 Yang CH, Cristofanilli M: Systemic treatments for inflammatory breast cancer. *Breast Dis.* 22, 55–65 (2005).

47 Jones SF, Hainsworth JD, Spigel DR *et al.*: A Phase I study of the dual kinase inhibitor GW572016 in combination with paclitaxel (EGF10009). *J. Clin. Oncol.* (Meeting Abstracts) 22 (2004) (Abstract 2083).

48 Johnston S, Trudeau M, B Kaufman *et al.*: Phase II study of predictive biomarker profiles for response targeting human epidermal growth factor receptor 2 (HER-2) in advanced inflammatory breast cancer with lapatinib monotherapy. *J. Clin. Oncol.* 26, 1066–1072 (2008).

49 Cristofanilli M, Boussen H, Baselga J: A Phase II combination study of lapatinib and paclitaxel as neoadjuvant therapy in patients with newly diagnosed inflammatory breast cancer (IBC). *Breast Cancer Res. Treat.* 100, S5 (2006) (Abstract 1).

50 Bonnefoi H, Zaman K, Nobahar M *et al.*: Lapatax: a Phase I study of neoadjuvant lapatinib combined with docetaxel in Her2/neu overexpressing breast cancer (BC). EORTC protocol 10054. Presented at: *San Antonio Breast Cancer Conference.* San Antonio, TX, USA, December 10–14 (2008) (Abstract 5112).

51 Bendell JC, Domchek SM, Burstein HJ *et al.*: Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer* 97, 2972–2977 (2003).

52 Clayton AJ, Danson S, S Jolly *et al.*: Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. *Br. J. Cancer* 91, 639–643 (2004).

53 Lin NU, Bellon JR, Winer EP: CNS metastases in breast cancer. *J. Clin. Oncol.* 22, 3608–3617 (2004).

54 Park IH, Ro J, Lee KS, Nam BH, Kwon Y, Shin KH: Trastuzumab treatment beyond brain progression in HER2-positive metastatic breast cancer. *Ann. Oncol.* 20, 56–62 (2009).

55 Pestalozzi BC, Brignoli S: Trastuzumab in CSF. *J. Clin. Oncol.* 18, 2349–2351 (2000).

56 Yau T, Swanton C, Chua S *et al.*: Incidence, pattern and timing of brain metastases among patients with advanced breast cancer treated with trastuzumab. *Acta Oncol.* 45, 196–201 (2006).

57 Stemmler HJ, Schmitt M, Willems A, Bernhard H, Harbeck N, Heinemann V: Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood–brain barrier. *Anticancer Drugs* 18, 23–28 (2007).

58 Lin NU, Carey LA, Liu MC *et al.*: Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. *J. Clin. Oncol.* 26, 1993–1999 (2008).

59 Lin NU, Dieras V, Paul D *et al.*: EGF105084, a Phase II study of lapatinib for brain metastases in patients (pts) with HER2$^+$ breast cancer following trastuzumab (H) based systemic therapy and cranial radiotherapy (RT). *J. Clin. Oncol.* (Meeting Abstracts) 25 (2007) (Abstract 1012).

60 Lin N, Paul D, Dieras V *et al.*: Lapatinib and capecitabine for the treatment of brain metastases in patients with HER2$^+$ breast cancer an updated analysis from EGF105084. *Breast Cancer Res. Treat.* 106 (2007) (Abstract 6076).

61 Massarweh S, Osborne CK, Creighton CJ *et al.*: Tamoxifen resistance in breast tumors is driven by growth factor receptor signaling with repression of classic estrogen receptor genomic function. *Cancer Res.* 68, 826–833 (2008).

62 Chu I, Blackwell K, Chen S, Slingerland J: The dual ErbB1/ErbB2 inhibitor, lapatinib (GW572016), cooperates with tamoxifen to inhibit both cell proliferation- and estrogen-dependent gene expression in antiestrogen-resistant breast cancer. *Cancer Res.* 65, 18–25 (2005).

63 Schiff R, Massarweh SA, Shou J, Bharwani L, Mohsin SK, Osborne CK: Cross-talk between estrogen receptor and growth factor pathways as a molecular target for overcoming endocrine resistance. *Clin. Cancer Res.* 10, 331S–336S (2004).

64 Chu QS, Cianfrocca ME, Goldstein LJ *et al.*: A Phase I and pharmacokinetic study of lapatinib in combination with letrozole in patients with advanced cancer. *Clin. Cancer Res.* 14, 4484–4490 (2008).

65 Johnston S, Pegram M, M Press M *et al.*: Lapatinib combined with letrozole vs letrozole alone for front line postmenopausal hormone receptor positive (HR$^+$) metastatic breast cancer (MBC): first results from the EGF30008 Trial. Presented at: *San Antonio Breast Cancer Symposium.* San Antonio, TX, USA, December 10–14 (2008) (Abstract 46).

66 Cardoso F, Koch K, Awada A *et al.*: Pharmacokinetics and tolerability of lapatinib administered once daily in combination with tamoxifen. Presented at: *San Antonio Breast Cancer Symposium*. San Antonio, TX, USA, December 10–14 (2008) (Abstract 2073).

67 Wolff AC, Hammond ME, Schwartz JN *et al.*: American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J. Clin. Oncol.* 25, 118–145 (2007).

68 Colomer R, Montero S, A Lluch A *et al.*: Circulating HER2 extracellular domain and resistance to chemotherapy in advanced breast cancer. *Clin. Cancer Res.* 6, 2356–2362 (2000).

69 Yamauchi H, A O'Neill, Gelman R *et al.*: Prediction of response to antiestrogen therapy in advanced breast cancer patients by pretreatment circulating levels of extracellular domain of the HER-2/c-neu protein. *J. Clin. Oncol.* 15, 2518–2525 (1997).

70 GlaxoSmithKline: Tykerb® package insert. Research Triangle Park, NC, USA (2009).

71 Le QA, Hay JW: Cost–effectiveness analysis of lapatinib in HER-2-positive advanced breast cancer. *Cancer* 115, 489–498 (2008).

72 DeLea T, Tappenden P, Sofrygin O *et al.*: Cost–effectiveness (CE) of lapatinib plus capecitabine (L + C) in women with HER2+ metastatic breast cancer (MBC) who received prior therapy with trastuzumab (TZ) based on updated survival data from EGF100151. *J. Clin. Oncol.* (Meeting Abstracts) 26 (2008) (Abstract 6559).

73 Marty M, Cognetti F, D Maraninchi *et al.*: Randomized Phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J. Clin. Oncol.* 23, 4265–4274 (2005).

74 Smith, IE: Efficacy and safety of Herceptin in women with metastatic breast cancer: results from pivotal clinical studies. *Anticancer Drugs* 12(Suppl. 4), S3–10 (2001).

75 Slamon DJ, Leyland-Jones B, Shak S *et al.*: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N. Engl. J. Med.* 344, 783–792 (2001).

76 Montemurro F, Donadio M, Clavarezza M *et al.*: Outcome of patients with HER2-positive advanced breast cancer progressing during trastuzumab-based therapy. *Oncologist* 11, 318–324 (2006).

77 Von Minckwitz G, Zielinski C, Maarteense E *et al.*: Capecitabine vs. capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP Phase III study (GBG 26/BIG 3–05). *J. Clin. Oncol.* 26, 1025 (2008).

78 Storniolo AM, Pegram MD, Overmoyer B *et al.*: Phase I dose escalation and pharmacokinetic study of lapatinib in combination with trastuzumab in patients with advanced ErbB2-positive breast cancer. *J. Clin. Oncol.* 26, 3317–3323 (2008).

79 Dickler M, Franco S, Stopeck A *et al.*: Final results from a Phase II evaluation of lapatinib (L) and bevacizumab (B) in HER2-overexpressing metastatic breast cancer (MBC). Presented at: *San Antonio Breast Cancer Conference.* San Antonio, TX, USA, December 10–14 (2008) (Abstract 3133).

80 Guarneri V, Frassoldati A, K Cagossi *et al.*: CHER LOB Trial: Preoperative chemotherapy plus trastuzumab, lapatinib or both in HER2-positive operable breast cancer – Safety report as per Independent Data Monitoring Committee (IDMC) and preliminary activity data. *J. Clin. Oncol.* (Meeting Abstracts) 26 (2008) (Abstract 580).

Websites

101 FDA, Drug infomation Approval for NDA 22–059 (2007)
www.fda.gov/cder/foi/nda/2007/022059s000TOC.htm

102 ClinicalTrials.gov. Docetaxel and lapatinib with or without combination chemotherapy or docetaxel and trastuzumab with combination chemotherapy in treating women with locally advanced, inflammatory, or resectable breast cancer
http://clinicaltrials.gov/ct2/show/NCT00450892
(Accessed February 2009)

103 ClinicalTrials.gov. Lapatinib and temozolomide for the treatment of progressive brain disease in HER-2 positive breast cancer (LAPTEM)
http://clinicaltrials.gov/ct2/show/NCT00614978
(Accessed February 2009)

104 ClinicalTrials.gov. Lapatinib plus capecitabine versus trastuzumab plus capecitabine in ErbB2 (HER2) positive metastatic breast cancer
http://clinicaltrials.gov/ct2/show/NCT00820222
(Accessed February 2009)

105 NICE Guidelines
www.nice.org.uk/Guidance/TA/Wave13/1
(Accessed February 2009)

106 AGO Group's breast cancer guidelines – Germany (2008)
www.ago-online.org/download/24TargetedTreatment.pdf

107 NCCN Practice Guidelines in Oncology – breast cancer v.2.2007
http://nccn.org/professionals/physician_gls/PDF/breast.pdf

108 ClinicalTrials.gov. Tykerb Evaluation After Chemotherapy (TEACH): lapatinib versus placebo in women with early-stage breast cancer
http://clinicaltrials.gov/ct2/show/NCT00374322
(Accessed February 2009)

109 ClinicalTrials.gov. ALTTO (Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation) Study; BIG 2–06/N063D
http://clinicaltrials.gov/ct2/show/NCT00490139
(Accessed February 2009)

110 ClinicalTrials.gov. Neo ALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) Study
http://clinicaltrials.gov/ct2/show/NCT00553358
(Accessed February 2009)