EJC SUPPLEMENTS 6, NO. 5 (2008) 15–24

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Promises borne out in clinical studies

*David Cameron**

National Cancer Research Network, Leeds, United Kingdom

ARTICLE INFO

Keywords:
Breast neoplasms
Lapatanib
Receptor, epidermal growth factor
HER2

ABSTRACT

This article reviews lapatinib clinical trials in patients with HER2 (ErbB2)-positive breast cancer, and is a report of a presentation from a symposium at the ECCO 14 congress in 2007.

Promising clinical results have been achieved to date with lapatinib, an oral, intracellular, dual-targeted small molecule inhibitor of EGFR (ErbB1) and HER2 in patients with HER2-positive metastatic breast cancer. Lapatinib has shown impressive activity in HER2-positive metastatic breast cancer, both first-line and in heavily pretreated patients whose disease has progressed following prior treatment in the metastatic setting with taxanes, anthracyclines and trastuzumab. Lapatinib has also demonstrated activity in inflammatory breast cancer, a particularly aggressive form of the disease. Lapatinib is generally well tolerated, with the most common adverse events being diarrhoea and rash, which can be effectively managed with proactive guidelines.

In conclusion, these data demonstrate that lapatinib is a promising new agent in the fight against HER2-positive breast cancer.

© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

A major unmet clinical need currently exists in the treatment of patients with HER2 (ErbB2)-positive metastatic breast cancer. Despite the real benefits seen in the clinic with the targeted agent trastuzumab,[1–3] therapeutic challenges still remain with respect to providing these patients with the most effective management strategies. Notably, as already discussed in the preceding article by Dr Christian Jackisch, a significant number of patients either do not respond to trastuzumab therapy,[1–3] or experience disease progression within 1 year.[1–4] Until recently, there were no proven anti-HER2 therapeutic options for these patients.

The oral, small-molecule dual-targeted inhibitor lapatinib has been developed in an effort to fulfil this unmet need. Lapatinib acts by reversibly and potently inhibiting the receptor tyrosine kinase activity of both the EGFR (ErbB1) and HER2 receptors.[5,6] *In vitro* experiments have demonstrated that lapatinib selectively acts against tumour cells without affecting normal cells.[5] Lapatinib is also capable of inhibiting the growth of HER2-overexpressing human breast tumour cells and xenografts.[5,7] Furthermore, lapatinib is also a potent inhibitor of human breast cancer cell lines that are insensitive to trastuzumab.[8]

The promising preclinical results obtained with lapatinib led to the initiation of Phase I clinical trials. These Phase I investigations demonstrated that lapatinib is well tolerated both as a monotherapy[9] and in combination with chemotherapeutic agents, with preliminary evidence of antitumour efficacy.[10,11] These Phase I trials also determined the optimum

*Address for correspondence: David Cameron. Director of NCRN, National Cancer Research Network Coordinating Centre, 24 Hyde Terrace, Leeds, LS2 9LN, UK.
Tel.: +44 113 343 8033; fax: +44 113 343 2242.
E-mail address: d.cameron@ncrn.org.uk (D. Cameron).

1359-6349/ $ – see front matter © 2008 Elsevier Ltd. All rights reserved.

Table 1 – Most common adverse event occurrence in a Phase II randomized study of lapatinib as a first-line treatment for patients with HER2-positive locally advanced or metastatic breast cancer [16]

Adverse event (N, %)	Lapatinib group	Grade 1–2 (n)	Grade 3 (n)
Diarrhoea (64/138, 46%)	1500 mg QD	29	2
	500 mg BID	29	4
Rash (44/138, 32%) [a]	1500 mg QD	22	0
	500 mg BID	20	1
Pruritus (31/138, 22%)	1500 mg QD	15	0
	500 mg BID	16	0
Back pain (20/138, 14%)	1500 mg QD	11	0
	500 mg BID	9	0
Vomiting (20/138, 14%)	1500 mg QD	10	2
	500 mg BID	7	1
Nausea (19/138, 14%)	1500 mg QD	10	0
	500 mg BID	8	1
Cough (18/138, 13%)	1500 mg QD	7	0
	500 mg BID	10	1

[a] One additional event of acne was reported with an unknown National Cancer Institute Common Toxicity Criteria grade.
No grade 4 events were reported. BID = twice daily; QD = once daily.

tolerated regimens for these lapatinib combinations for further evaluation in Phase II/III trials in patients with HER2-positive metastatic breast cancer. Clinical activity has since been confirmed in patients pretreated with trastuzumab in the metastatic setting who received lapatinib in combination with capecitabine in a pivotal Phase III trial. [12,13] Lapatinib is also being evaluated in combination with paclitaxel in Phase II/III trials as a first-line treatment in patients with metastatic HER2-positive breast cancer, [14] in combination with endocrine agents and trastuzumab, and as a neoadjuvant treatment for inflammatory breast cancer (IBC) [15] and large operable breast cancer. This article summarizes the findings of those clinical trials that have been reported in patients with HER2-positive breast cancer.

2. Early clinical experience with lapatinib

Initial proof-of-concept studies conducted with lapatinib monotherapy have demonstrated that this oral, dual-targeted EGFR and HER2 inhibitor is a relatively well tolerated and effective treatment for patients with HER2-positive metastatic breast cancer. Gomez and colleagues conducted a Phase II trial that investigated the efficacy and safety of lapatinib monotherapy as a first-line treatment in patients with HER2-positive advanced or metastatic breast cancer. Patients received either 1500 mg once-daily (QD) or 500 mg twice-daily (BID) oral (po) lapatinib for a minimum of 12 weeks. The overall response rate (ORR; including both complete responses [CR] and partial responses [PR]) was 24% and the clinical benefit rate (CR, PR and patients with stable disease for $\geqslant$24 weeks) was 31.2%. [16] These response rates are not dissimilar from those reported in a study of trastuzumab monotherapy in a similar group of patients with HER2-positive metastatic breast cancer. [16–18] However, definitive conclusions on the comparative efficacy of both drugs can only be made following an appropriately designed head-to-head randomized clinical trial.

The results of the Phase II trial conducted by Gomez and colleagues also demonstrated that lapatinib monotherapy is well tolerated in patients with HER2-positive advanced or metastatic breast cancer, with the majority of adverse events (AEs) being grade 1 or 2 (Table 1). The most commonly reported AE was diarrhoea (46% of patients), although only six patients (4%) experienced a grade 3 episode. Overall incidence of rash was 32% and only one patient from the 500 mg BID group experienced a grade 3 rash. No grade 4 episodes were reported for any AE and no clinically significant cardiac events were reported in this trial. [16]

3. Clinical experience with lapatinib plus chemotherapy in patients pretreated with trastuzumab – the EGF100151 study

An initial Phase I trial identified the optimum tolerated lapatinib plus capecitabine regimen and found that this combination was relatively well tolerated in previously treated patients with advanced solid malignancies, with preliminary evidence of antitumour activity. [10] Two of

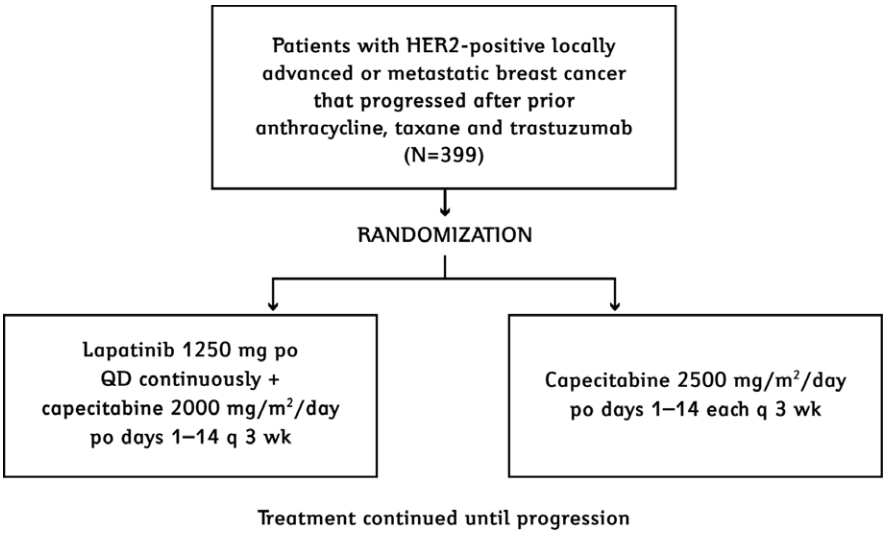

Fig. 1 – Study design for the EGF100151 clinical trial. [13] **po = oral administration; QD = once daily; q 3 wk = once every three weeks.**

the four confirmed responses occurred in patients with advanced breast cancer, including the only CR observed in this trial and one of the three confirmed PRs. [10] Based on these promising Phase I results, a Phase III trial (EGF100151) was conducted to further evaluate the efficacy and tolerability of lapatinib in combination with capecitabine in patients with HER2-positive advanced or metastatic breast cancer pretreated with a taxane, an anthracycline and trastuzumab. [12,13] Capecitabine monotherapy was used as the comparator arm in this trial. [12,13] This pivotal trial was the first randomized, controlled, prospective study to report on the efficacy of continuing HER2-suppression following one line of a trastuzumab-containing regimen in patients with advanced breast cancer. [12,13] Previous analyses of continued HER2-suppression by re-treating patients with trastuzumab following at least one line of a trastuzumab-containing regimen have only been retrospective, and thus are subject to the limitations of that type of study. [19] Very recently, the interim results were reported of a prospective study of trastuzumab plus capecitabine versus capecitabine alone in a similar patient group (i.e., patients with HER2-positive metastatic breast cancer whose disease had progressed while on trastuzumab-containing regimens in the metastatic setting). [20] This latter study was closed early due to poor accrual and, therefore, with only 152 of a planned 482 patients randomized, remains underpowered. While median TTP was longer in the trastuzumab and capecitabine versus capecitabine monotherapy arm (at 33 and 24 weeks, respectively), this between-treatment difference was not statistically significant. [20]

Patients in the EGF100151 study were randomized 1:1 to treatment with either capecitabine monotherapy or lapatinib and capecitabine, as shown in Figure 1. [12] The primary endpoint of the trial was time to progression (TTP), based on an evaluation performed by independent reviewers under blinded conditions. [12,13]

3.1. Study EGF100151 eligibility and HER2 status

Eligible patients were aged $\geqslant$18 years, and had confirmed HER2-positive locally advanced or metastatic breast cancer, with a life expectancy of at least 12 weeks, and must have received previous treatment with an anthracycline-, taxane- and a trastuzumab-containing regimen. HER2 positivity was confirmed using local laboratories, and patients were considered to have HER2-positive disease if they had grade 3+ immunohistochemical (IHC) staining intensity (on a scale of 0 to 3) or grade 2+ staining intensity and positive gene amplification results following fluorescence *in situ* hybridization (FISH). Patients were also required to have measurable disease according to the Response Evaluation Criteria In Solid Tumours (RECIST), an Eastern Cooperative Oncology Group performance status of 0 or 1, and if present, stable brain metastases. [12]

3.2. Study EGF100151 efficacy – interim analysis

A pre-planned interim analysis was performed after 121 disease progression events (49 events in the combination group and 72 events in the monotherapy group). [12] This interim analysis, based on independently reviewed assessment of progression, demonstrated that the TTP was significantly longer for patients who received the combination than for those treated with capecitabine alone ($p < 0.001$). [12] This improvement in efficacy was achieved without an increase in serious toxic effects or symptomatic cardiac events. [12] Based on achievement of the primary study endpoint and the acceptable safety profile achieved with the use of lapatinib and capecitabine, the Independent Data

Table 2 – Key efficacy data from the EGF100151 Phase III study of lapatinib plus capecitabine versus capecitabine alone in patients with HER2-positive advanced or metastatic breast cancer pretreated with a taxane, an anthracycline and trastuzumab [13]

	Lapatinib + capecitabine (N = 198)	Capecitabine (N = 201)	HR (95% CI)	OR (95% CI)	p-value
Median TTP, months	6.2	4.3	0.57 (0.43, 0.77)	n/a	0.00013
ORR (%)	23.7	13.9	n/a	1.9 (1.1, 3.4)	0.017
CR (%)	<1	0	n/a	–	–
PR (%)	23	14	n/a	–	–
Median OS, months	15.6	15.3	0.78 (0.55,1.12)	n/a	0.177

HR = hazard ratio; n/a = not applicable; OR = odds ratio; ORR = overall response rate (complete [CR] or partial response [PR]); OS = overall survival; TTP = time to progression.

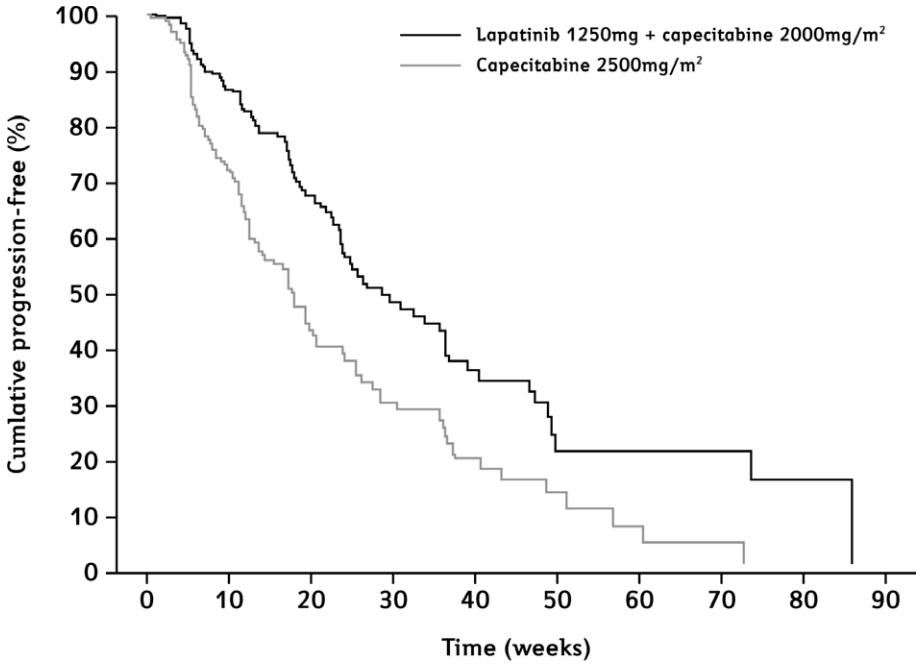

Fig. 2 – Time to progression with lapatinib plus capecitabine versus capecitabine monotherapy in patients with HER2-positive locally advanced or metastatic breast cancer (EGF100151 clinical trial). [13] Reproduced from Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib 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* 2008, Epub ahead of print, with kind permission of Springer Science and Business Media. CI = confidence interval; HR = hazard ratio; TTP = time to progression.

Monitoring Committee (IDMC) recommended that the trial be prematurely halted and all the patients in the monotherapy arm be allowed to select their preferred treatment option. [12]

3.3. Study EGF100151 efficacy – updated analysis

The interim study results were supported by a recently published updated analysis (Table 2). [13] This updated analysis showed that the statistically significant improvement in TTP with lapatinib combination treatment compared with capecitabine monotherapy was maintained, with a hazard ratio of 0.57 (95% confidence interval [CI]: 0.43, 0.77; p = 0.00013; medians of 6.2 months [27.1 weeks] versus 4.3 months [18.6 weeks], respectively; Figure 2). [13] The ORR was also significantly greater for the combination treatment compared with capecitabine monotherapy (23.7 versus 13.9%, respectively; odds ratio 1.9 [95% CI: 1.1, 3.4]; p = 0.017). [13] The positive responses observed are all the more encouraging, bearing in mind

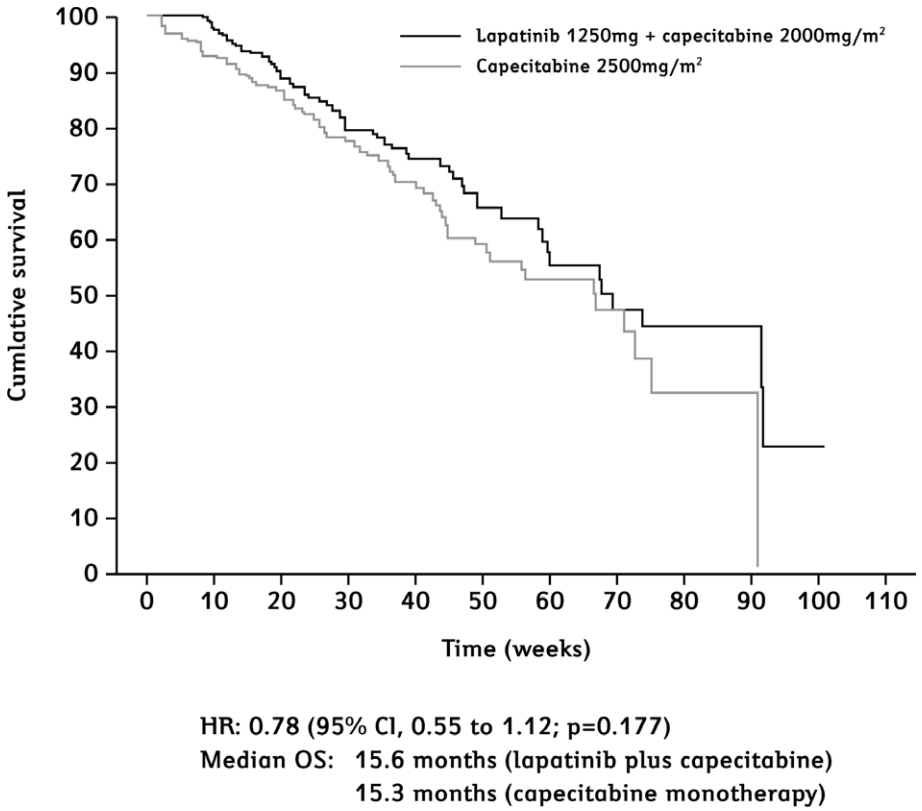

Fig. 3 – Overall survival with lapatinib plus capecitabine versus capecitabine monotherapy in patients with HER2-positive locally advanced or metastatic breast cancer (EGF100151 clinical trial).[13] Reproduced from Cameron D, Casey M, Press M et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses, *Breast Cancer Res Treat* 2008, Epub ahead of print, with kind permission of Springer Science and Business Media. CI = confidence interval; HR = hazard ratio; OS = overall survival.

that the trial was conducted in a heavily pretreated and difficult-to-treat patient population. It must be acknowledged that the design of the EGF100151 study was based on the principle of continuing chemotherapy until progression (or the patient's wish to stop), rather than the more common UK and European approach of administering a fixed number of cycles. However, it must also be recognized that the use of a predetermined fixed number of chemotherapy cycles is less rigidly applied with capecitabine, even in the UK, as this drug is often better tolerated than many intravenous chemotherapies. What cannot be determined from the EGF100151 study, however, is whether stopping capecitabine after perhaps four or six cycles in the absence of progression, but continuing with lapatinib, would give similar levels of efficacy.

The original statistical design of the EGF100151 study gave sufficient power, if continued to the original planned accrual target of 528, to detect meaningful differences in overall survival (OS). However, since the study was closed prematurely following IDMC recommendation, it is underpowered to detect the original hypothesized differences in survival for the combination of lapatinib plus capecitabine versus capecitabine alone.[12,13] The more recent analysis of the study does show that there is a trend towards improvement in OS, with an HR that has decreased over time from 0.92 [95% CI: 0.58, 1.46] at the time of the pre-planned interim analysis, to 0.78 [95% CI: 0.55, 1.12] at this updated analysis 5 months later (Figure 3).[12,13] Furthermore, the lapatinib combination and capecitabine monotherapy survival curves separated early and remained separated throughout the study.

3.4. *Study EGF100151 safety*

The results of the EGF100151 trial indicated that the combination treatment was well tolerated and the use of lapatinib plus capecitabine was not associated with an increase in serious AEs compared with capecitabine alone. The AEs encountered were mainly grade 1 or 2 and the incidence of grade 3 and 4 AEs was similar in both of the treatment arms.[13] No grade 4 episodes of rash or hand–foot syndrome were observed in patients that received either lapatinib plus capecitabine, or capecitabine alone.[13] Only two cases of grade 4 diarrhoea (1% of patients) were observed in the patients who received the combination treatment.[13] These data are

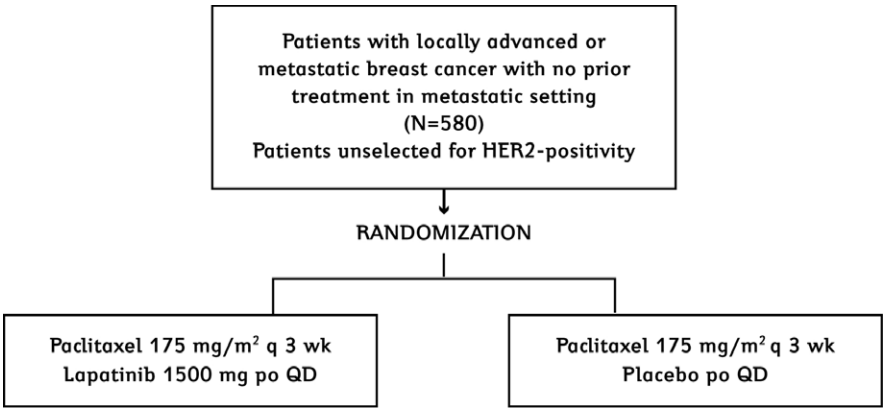

Fig. 4 – Study design for the EGF30001 clinical trial.[14] po = oral administration; QD = once daily; q 3 wk = once every three weeks.

similar to the results of a pooled analysis of lapatinib clinical trials involving >2000 patients with advanced or metastatic tumours (including five trials in breast cancer), in which the incidence of grade 4 diarrhoea was ⩽1% and most events occurred early in the course of treatment.[21]

The occurrence of cardiac AEs is a potential concern with agents that inhibit HER2;[22] however, no patients discontinued treatment due to a decrease in left ventricular ejection fraction (LVEF) in the EGF100151 trial.[12,13]

3.5. *Study EGF100151 summary*

The EGF100151 trial has provided the first Level 1 evidence (Oxford criteria)[23] supporting the clinical efficacy of continued anti-HER2 targeted therapy in patients with HER2-positive advanced or metastatic breast cancer, whose disease is progressing following prior therapy with anthracyclines, taxanes and trastuzumab in the metastatic setting. Moreover, the findings of the EGF100151 clinical trial have resulted in lapatinib plus capecitabine being the only treatment option recommended for such patients with HER2-positive advanced or metastatic breast cancer, in recent national guidelines.[24,25]

4. Clinical experience with lapatinib plus chemotherapy as first-line treatment of HER2-positive advanced or metastatic breast cancer

Another pivotal Phase III trial (EGF30001) has evaluated the combination of lapatinib with paclitaxel versus placebo plus paclitaxel as a first-line treatment in patients with advanced or metastatic breast cancer (Figure 4). This randomized, controlled trial was designed to test the hypothesis that this combination might be effective in HER2-negative breast cancer patients, since those with known HER2-positive disease would be candidates for the combination of paclitaxel and trastuzumab. Thus, the inclusion criteria made HER2-negative patients the main focus of this trial. However, at the time of enrolment, the HER2 status of some enrolled patients was not known, but the primary analyses focused on the overall breast cancer patient population.[14] Subsequent central pathology review identified that there were some patients enrolled who were HER2-positive (as per standard IHC and FISH performed on tumour biopsies), and a subgroup analysis was then performed on this cohort.[14]

4.1. *EGF30001 eligibility and HER2 status*

Patients were suitable for enrolment into the EGF30001 trial if they had incurable Stage IIIb, IIIc or IV disease, no prior treatment for breast cancer in the metastatic setting and either HER2-negative or untested disease. A diagnosis of HER2-negative disease was confirmed by IHC (grade 0 or 1+) or a negative result using FISH analysis. The primary endpoint of the trial was TTP in order to measure the possible benefit of intervention with lapatinib plus paclitaxel versus paclitaxel monotherapy.[14]

4.2. *EGF30001 efficacy – primary analysis in overall patient population*

In the primary analysis in the total patient population, there was no significant difference between treatment groups in the primary endpoint, median TTP (6.7 months for the combination versus 5.3 months for paclitaxel plus placebo; hazard ratio 0.87 [95% CI: 0.72, 1.05]; p = 0.142).[14]

4.3. *EGF30001 efficacy – HER2-positive patient subgroup analysis*

Tumour samples were available from 531 enrolled patients, allowing the HER2 status to be confirmed by a central laboratory. Amongst these, 91 were found to be HER2-positive (52 [19%] in the lapatinib combination arm, and 39 [15%] treated with paclitaxel plus placebo);

Table 3 – Key efficacy data from the EGF30001 Phase III study of lapatinib plus paclitaxel versus paclitaxel alone as first-line treatment in patients with HER2-positive advanced or metastatic breast cancer [14]

	Lapatinib + paclitaxel (n = 52)	Paclitaxel (n = 39)	HR (95% CI)	p-value
Median TTP, months	8.1	5.8	0.57 (0.34, 0.93)	0.011
ORR, %	60	36	n/a	0.027
Median OS, months	24.0	19.0	0.64 (0.3,1. 2)	0.160

CI = confidence interval; HR = hazard ratio; n/a = not applicable; ORR = overall response rate (complete [CR] or partial response [PR]); OS = overall survival; TTP = time to progression.

all of these patients were included in the HER2-subgroup analysis. [14] The subgroup analysis demonstrated that, in contrast to the overall population, median TTP was significantly prolonged in HER2-overexpressing patients treated with lapatinib plus paclitaxel compared with paclitaxel alone (35.1 versus 25.1 weeks [or 8.1 versus 5.8 months]; hazard ratio 0.57 [95% CI: 0.34, 0.93] p = 0.011) (Table 3). [14] The ORR was also significantly higher with lapatinib combination treatment compared with paclitaxel alone (60 versus 36%; p = 0.027). [14] There was also a trend for an improvement in median OS, at 24.0 months with lapatinib compared with 19.0 months with paclitaxel plus placebo treatment. However, this difference in OS was not statistically significant (hazard ratio 0.64 [95% CI: 0.3, 1.2]; p = 0.160). [14]

4.4. *EGF30001 safety – overall patient population*

The lapatinib plus paclitaxel combination treatment was well tolerated in the overall study population evaluated in the EGF30001 trial, with the majority of AEs being grade 1–2. [14] The incidences of rash (44% versus 22%, respectively), diarrhoea (58% versus 26%), vomiting (25% versus 17%) and mucositis (13% versus 3%) of any grade were higher for the lapatinib combination compared with paclitaxel alone. [14] However, there was little difference between the lapatinib combination and paclitaxel groups in the incidences of grade 3 or 4 rash (4/0% versus 0/0%, respectively), vomiting (2/0% versus 1/0%) and mucositis (1/<1% in both groups). [14]

In the EGF30001 study, $\geqslant$20% decreases in LVEF, grade 4 laboratory abnormalities and grade 3/4 cardiac dysfunction or pneumonitis were classed as serious AEs, along with the standard International Conference on Harmonisation Good Clinical Practice (ICH-GCP) definitions. The overall incidence of serious AEs was 35% with lapatinib combination and 22% with paclitaxel plus placebo treatment. [14] There were no significant differences in the incidences of serious neutropenia (8% versus 5%, respectively), febrile neutropenia (3% versus 1%) and decreases in LVEF (2% versus 2%) between the lapatinib- and paclitaxel-containing regimens. [14] Importantly, the incidence of a $\geqslant$20% decrease in LVEF of any grade was identical in the lapatinib combination and the paclitaxel monotherapy groups (2%), and there were no grade 3 or 4 decreases in LVEF. [14]

The incidence of grade 3 or 4 diarrhoea was higher with the lapatinib combination compared with paclitaxel alone (15/<1% versus 1/0%, respectively). [14] Similarly, the incidence of serious diarrhoea, although low, was significantly higher with the lapatinib combination than paclitaxel plus placebo (8% versus <1%, respectively; p < 0.0001). [14] The incidence of serious AEs leading to death also appeared higher with the lapatinib combination than with paclitaxel plus placebo treatment (2.7% versus 0.6%, respectively). However, the introduction of diarrhoea management guidelines resulted in an improvement in the management of lapatinib-combination side effects during this trial and a reduction in the incidence of deaths due to serious AEs over time. [14]

A combined analysis of trials conducted to date evaluating lapatinib in combination with taxanes provides further evidence of a favourable safety profile for this combination. [26] The incidences of grade 3 or above diarrhoea, rash, neutropenia and febrile neutropenia were 18%, 5%, 15% and 3%, respectively, and were manageable and of short duration. [26] The severity of these diarrhoea and skin events can be reduced if the relevant AE management guidelines are adopted, [27,28] which is reflected in the observation in this combined analysis that higher incidences of these AEs were seen in earlier studies prior to implementation of such AE management guidelines. [26]

4.5. *Relative efficacy of lapatinib plus a taxane as first-line treatment of HER2-positive advanced or metastatic breast cancer*

A comparison of the results of the EGF30001 subgroup analysis with published trial data suggests that lapatinib plus paclitaxel appears to be of similar efficacy compared with trastuzumab plus a taxane (paclitaxel or docetaxel) in treating HER2-positive metastatic breast cancer. [1–3,14] The reported ORR (60% versus 49%, respectively), median TTP (8.1 versus 7.1 months) and OS (24.0 versus 24.8 months) values were similar in the HER2-positive cohort of the EGF30001 trial and a published retrospective subgroup analysis of trastuzumab combined with an

identical dose of paclitaxel as first-line therapy.[2,14] The ORR with lapatinib plus paclitaxel in the EGF30001 trial HER2-positive cohort also compares favourably with the reported ORR for trastuzumab plus docetaxel (60% versus 61%, respectively) administered first line to patients with metastatic HER2-positive breast cancer.[1,14]

It is important to note that these are cross-trial comparisons and should be treated with caution. To enable definitive conclusions to be drawn on the relative efficacy of first-line anti-HER2 therapy with either lapatinib- or trastuzumab-based taxane combinations, the National Cancer Institute of Canada is conducting a head-to-head comparison of lapatinib versus trastuzumab, with both agents given in combination with paclitaxel or docetaxel. This study (EGF108919) is due to be initiated in 2008 and will have as its primary endpoint progression-free survival, and secondary endpoints that include: OS; incidence of, and time to, central nervous system metastasis as first progression; ORR; clinical benefit rate; and safety.

5. Lapatinib combination therapy for the treatment of patients with inflammatory breast cancer

Inflammatory breast cancer represents 1–5% of all breast cancer cases, and is often associated with HER2 overexpression;[29,30] up to 52% of patients with IBC may be HER2-positive, based on tumour biopsy data.[29] IBC is the most aggressive form of breast cancer[31,32] and, despite treatment advances, its management remains a significant challenge.[33]

Initial clinical studies have, therefore, been conducted to evaluate the efficacy of lapatinib in combination with paclitaxel for the treatment of patients with IBC.

In one study, patients with both HER2-positive (n = 30) and HER2-negative (n = 5) breast cancer received neoadjuvant chemotherapy prior to surgery and adjuvant therapy.[15] The neoadjuvant regimen was lapatinib (1500 mg QD po) for 2 weeks followed by a further 12 weeks of lapatinib plus paclitaxel (80 mg/m^2 every week). Tumour biopsies were taken from patients prior to initiating the study and after the first 2 weeks of treatment.

An ORR of 77% was obtained in the HER2-positive patients, and 80% in the HER2-negative patients, an impressive result in this highly refractory population.[15] It is important to note that these data are preliminary and further analyses are ongoing. However, these results highlight the potency of lapatinib in the treatment of HER2-positive breast cancer.

6. Clinical safety with lapatinib

The main AEs associated with the use of lapatinib to date across clinical trials are diarrhoea and rash. However, the incidence of both of these events is predictable and can be easily managed by adopting safety management guidelines.

The use of kinase inhibitors that target the EGFR cell surface receptor is known to be associated with low-grade gastrointestinal events, including diarrhoea.[34,35] Similarly, the occurrence of skin events, which include skin, hair and nail toxicities, is common, and thought to be related to the inhibition of EGFR in the epidermis.[36–38] The manufacturers of lapatinib, GlaxoSmithKline, have, therefore, produced rash and diarrhoea guidelines in order to proactively manage these predictable AEs. The rash guidelines were developed by GlaxoSmithKline physicians, whereas the diarrhoea management guidelines are based on the recommendations stipulated by the American Society of Clinical Oncology (ASCO) for the treatment of cancer-treatment induced diarrhoea.[27]

Clinical trials conducted to date with lapatinib demonstrate that the use of this agent is associated with a low risk of cardiac AEs, as confirmed by a recent meta-analysis in 3127 patients.[39] In these trials, LVEF was monitored every 8 weeks using MUGA or echocardiogram.[39] The results of this meta-analysis demonstrated that the incidence of LVEF decrease (1.3%; n = 42) in lapatinib-treated patients was no higher than in the general breast cancer patient population (3–6%).[39,40] Additionally, symptomatic events were extremely rare, occurring in four of 42 patients (0.1% incidence).[39] Decreases in LVEF occurred within 9 weeks of treatment onset in 69% of cases.[39] The events resolved in 62% of cases and lapatinib was continued in 42% of these.[39] The average duration of LVEF decreases was 4 weeks.[39] These LVEF decreases were manageable with most symptomatic events responding promptly to standard congestive heart failure therapy. Also, the majority of patients who experienced an LVEF decrease (90%) had confounding factors that may have contributed to the event.[39]

7. Conclusions

Promising clinical results have been achieved to date with lapatinib in patients with HER2-positive breast cancer in a variety of settings. Beneficial responses have been observed when lapatinib is used both as a monotherapy and in combination with chemotherapeutic agents. Importantly, lapatinib is the only agent in development that has Level 1 evidence of clinical efficacy in patients with HER2-positive advanced or metastatic breast cancer following one line of a trastuzumab-containing regimen. This has prompted some national guideline authorities to recommend the use of lapatinib plus capecitabine in treating patients with HER2-positive breast cancer.[24,25] An extensive clinical development programme is currently underway for lapatinib, across all lines of therapy, to thoroughly investigate its

role in treating patients with HER2-positive breast cancer. These ongoing lapatinib trials are overviewed in an accompanying article in this supplement by Dr Pierre Fumoleau.

Acknowledgments

The author would like to thank Yasamin Mir-Shekari, DPhil, Medicus International, for her editorial assistance. Editorial support and publication of this supplement was funded by an unrestricted educational grant from GlaxoSmithKline.

Conflict of interest statement

The author has received honoraria from both GlaxoSmithKline and Roche, and research funding from Roche unrelated to the data presented in this article.

Role of the funding source

GlaxoSmithKline had no editorial control in respect of this article and the views expressed are solely those of the author.

References

1. Marty M, Cognetti F, Maraninchi D, 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* 2005;23(19):4265–74.
2. Smith IE. Efficacy and safety of Herceptin in women with metastatic breast cancer: results from pivotal clinical studies. *Anticancer Drugs* 2001;12(Suppl 4):S3–10.
3. 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* 2001;344(11):783–92.
4. Burstein HJ, Kuter I, Campos SM, et al. Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2001;19(10):2722–30.
5. Rusnak DW, Lackey K, Affleck K, et al. The effects of the novel, reversible epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor, GW2016, on the growth of human normal and tumor-derived cell lines in vitro and in vivo. *Mol Cancer Ther* 2001;1(2):85–94.
6. Wood ER, Truesdale AT, McDonald OB, et al. A unique structure for epidermal growth factor receptor bound to GW572016 (Lapatinib): relationships among protein conformation, inhibitor off-rate, and receptor activity in tumor cells. *Cancer Res* 2004;64(18):6652–9.
7. Rusnak DW, Affleck K, Cockerill SG, et al. The characterization of novel, dual ErbB-2/EGFR, tyrosine kinase inhibitors: potential therapy for cancer. *Cancer Res* 2001;61(19):7196–203.
8. 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* 2006;66(3):1630–9.
9. Burris 3rd HA, 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* 2005;23(23):5305–13.
10. 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* 2007;25(24):3753–8.
11. 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 ASCO Annual Meeting Proceedings* 2004;22(14 Suppl): Abstract #2083.
12. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355(26):2733–43.
13. Cameron D, Casey M, Press M, 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* 2008 Jan 11; Epub ahead of print.
14. Di Leo A, Gomez H, Aziz Z, et al. Lapatinib (L) with paclitaxel compared to paclitaxel as first-line treatment for patients with metastatic breast cancer: A phase III randomized, double-blind study of 580 patients. *J Clin Oncol ASCO Annual Meeting Proceedings* 2007;25(18S): Abstract #1011. Presentation available at: http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d / ?vgnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=47&abstractID=35691.
15. Cristofanilli M, Boussen H, Baselga J, et al. A phase II combination study of lapatinib and paclitaxel as a neoadjuvant therapy in patients with newly diagnosed inflammatory breast cancer (IBC). *Breast Cancer Res Treat* 2006;100(Suppl 1): Abstract #1.
16. Gomez HL, Chavez MA, Doval DC, et al. Updated biomarker results from a phase II randomized study of lapatinib as first-line treatment for patients with ErbB2-amplified advanced or metastatic breast cancer. *Breast Cancer Res Treat* 2006;100(Suppl 1): Abstract #1090.
17. Baselga J, Carbonell X, Castaneda-Soto NJ, et al. Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. *J Clin Oncol* 2005;23(10):2162–71.
18. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002;20(3):719–26.
19. Montemurro F, Donadio M, Clavarezza M, et al. Outcome of patients with HER2-positive advanced breast cancer progressing during trastuzumab-based therapy. *Oncologist* 2006;11(4):318–24.
20. von Minckwitz G, Vogel P, Schmidt M, et al. Trastuzumab treatment beyond progression in patients

with HER-2 positive metastatic breast cancer – the TBP study (GBG 26/BIG 3-05). *Breast Cancer Res Treat* 2007;106(Suppl 1): Abstract #4056.
21. Crown JP, Burris HA, Boyle F, et al. Pooled analysis of diarrhea events in patients with cancer treated with lapatinib. *Breast Cancer Res Treat* 2008 Jan 20; Epub ahead of print.
22. Yeon CH, Pegram MD. Anti-erbB-2 antibody trastuzumab in the treatment of HER2-amplified breast cancer. *Invest New Drugs* 2005;23(5):391–409.
23. Graham AJ, Gelfand G, McFadden SD, Grondin SC. Levels of evidence and grades of recommendations in general thoracic surgery. *Can J Surg* 2004;47(6):461–5.
24. AGO Group's breast cancer guidelines (Germany). Available at: http://www.ago-online.org/download/24TargetedTreatment.pdf.
25. NCCN Practice Guidelines in Oncology – breast cancer v.2.2007. Available at: http://nccn.org/professionals/physician_gls/PDF/breast.pdf.
26. Crown JP, Burris HA, Jones S, et al. Safety and tolerability of lapatinib in combination with taxanes (T) in patients with breast cancer (BC). *J Clin Oncol ASCO Annual Meeting Proceedings* 2007;25(18S): Abstract #1027. Presentation available at: http://www.asco.org/portal/site/ASCO/template.RAW/menuitem.34d60f5624ba07fd506fe310ee37a01d/?javax.portlet.tpst=0e116779df458209ada2be0aee37a01d_ws_RW&javax.portlet.prp_0e116779df458209ada2be0aee37a01d_viewID=abst_detail_rawview&javax.portlet.begCacheTok=com.vignette.cachetoken&javax.portlet.endCacheTok=com.vignette.cachetoken&index=n&confID=47&abstractID=35215.
27. Benson 3rd AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol* 2004;22(14):2918–26.
28. Moy B, Goss PE. Lapatinib-associated toxicity and practical management recommendations. *Oncologist* 2007;12(7):756–65.
29. Parton M, Dowsett M, Ashley S, Hills M, Lowe F, Smith IE. High incidence of HER-2 positivity in inflammatory breast cancer. *Breast* 2004;13(2):97–103.
30. Sawaki M, Ito Y, Akiyama F, et al. High prevalence of HER-2/neu and p53 overexpression in inflammatory breast cancer. *Breast Cancer* 2006;13(2):172–8.
31. van Golen KL, Davies S, Wu ZF, et al. A novel putative low-affinity insulin-like growth factor-binding protein, LIBC (lost in inflammatory breast cancer), and RhoC GTPase correlate with the inflammatory breast cancer phenotype. *Clin Cancer Res* 1999;5(9):2511–9.
32. Walshe JM, Swain SM. Clinical aspects of inflammatory breast cancer. *Breast Dis* 2005;22:35–44.
33. Wu M, Merajver SD. Molecular biology of inflammatory breast cancer: applications to diagnosis, prognosis, and therapy. *Breast Dis* 2005;22:25–34.
34. Johnson JR, Cohen M, Sridhara R, et al. Approval summary for erlotinib for treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. *Clin Cancer Res* 2005;11(18):6414–21.
35. Reck M, Buchholz E, Romer KS, Krutzfeldt K, Gatzemeier U, Manegold C. Gefitinib monotherapy in chemotherapy-naive patients with inoperable stage III/IV non-small-cell lung cancer. *Clin Lung Cancer* 2006;7(6):406–11.
36. Cersosimo RJ. Gefitinib: an adverse effects profile. *Expert Opin Drug Saf* 2006;5(3):469–79.
37. Gordon AN, Finkler N, Edwards RP, et al. Efficacy and safety of erlotinib HCl, an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor, in patients with advanced ovarian carcinoma: results from a phase II multicenter study. *Int J Gynecol Cancer* 2005;15(5):785–92.
38. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat Rev Cancer* 2006;6(10):803–12.
39. Perez EA, Byrne JA, Hammond IW, et al. Cardiac safety experience in 3127 patients (pts) treated with lapatinib. *Ann Oncol* 2006;17(Suppl 9): Abstract #1420.
40. Perez EA, Byrne JA, Hammond IW, et al. Results of an analysis of cardiac function in 2,812 patients treated with lapatinib. *J Clin Oncol ASCO Annual Meeting Proceedings* 2006;24(18S): Abstract #583.