Lapatinib: Current Status and Future Directions in Breast Cancer

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Abstract
Lapatinib is an oral receptor tyrosine kinase inhibitor, targeting both the ErbB-1 and ErbB-2 receptors. Preclinical in vitro and in vivo models indicate that lapatinib is active as monotherapy, synergistically in combination with trastuzumab, and in trastuzumab-resistant cell lines. Early clinical trials also provide evidence in patients that lapatinib is active against breast cancer. This paper reviews results of phase II and III clinical trials of lapatinib in metastatic breast cancer, evidence for its potential in patients with brain metastases, and current clinical trials as adjuvant treatment in early-stage disease. Our improved understanding of the biology of breast cancer and the use of biomarkers for identification of specific subtypes is allowing us to bring patient-specific novel therapies such as lapatinib to the clinic. The Oncologist 2006;11:1047–1057

Introduction
Breast cancer is frequently associated with increased expression and activation of the epidermal growth factor receptor (EGFR) tyrosine kinases (RTKs) that are involved in regulation of normal breast development [1–3]. Increased expression and activation of these RTKs are associated with a high risk for recurrence after primary treatment and consequently a poor clinical outcome [4]. RTKs provide docking sites for various adapter proteins and signaling enzymes which in turn activate various downstream signaling pathways [1, 5]. Pathways that can be activated via the ErbB family are shown in Figure 1. These events are linked to cell proliferation, survival, motility, etc. [1, 5]. Thus, inhibition of EGFRs could have an important antitumorigenic effect [1, 4, 5–9].

The EGFR or ErbB family of receptors includes four receptors, namely: EGFR/ErbB-1, HER-2/ErbB-2, HER-3/ErbB-3, and HER-4/ErbB-4 [1, 9, 10]. HER-1, or ErbB-1, overexpression occurs in about 27%–30% of breast tumors and HER-2, or ErbB-2, is overexpressed in an estimated 20%–25% of the 1.5 million new breast cancers that are diagnosed annually worldwide [1, 9, 11–19].

RTKs consist of an extracellular ligand-binding domain, a transmembrane domain in the lipid bilayer, and an intracellular cytoplasmic catalytic domain or protein tyrosine kinase (TK) domain [1, 20]. The receptors are not fixed in one place in the plasma membrane, and upon ligand binding to the extracellular domain, dimerization occurs. These dimers can be homodimers (i.e., two identical receptors, such as HER-1 and HER-1, etc.) or heterodimers (i.e., different receptors, such as HER-1 and HER-2, etc.) (Fig. 1) [1, 5, 9, 20, 21]. The type of partner in the dimerization is important because it impacts on the downstream effect [1]. Upon ligand binding and dimerization, the intracellular cytoplasmic TK domain is activated and autophosphorylation occurs (Fig. 2) [1, 5, 6].

Lapatinib ditosylate (GW572016/Tykerb®; GlaxoSmithKline, Research Triangle Park, NC) is an oral dual...
TK inhibitor targeting both the ErbB-1 and ErbB-2 receptors and has shown promising activity in preclinical investigations and clinical trials [22, 23]. Lapatinib works intracellularly and directly targets the TK domain. Lapatinib reversibly binds to the cytoplasmic ATP-binding site of the kinase and blocks receptor phosphorylation and activation, thereby preventing subsequent downstream signaling events, namely, simultaneous activation of extracellular signal–related kinase (ERK)-1/2 and phosphatidylinositol 3' kinase (PI3K)/Akt (Fig. 3) [22–26].

There are several theoretical advantages of a small molecule inhibitor of both ErbB-1 and ErbB-2 (i.e., lapatinib) compared with a monoclonal antibody that targets extracellular ErbB-2 only (i.e., trastuzumab, Herceptin®; Genentech, Inc., South San Francisco, CA). An inhibitor of one TK alone may not be as effective at inhibiting heterodimers containing both ErbB-1 and ErbB-2 [27]. An important additional theoretical advantage of the dual kinase inhibition activity of lapatinib over trastuzumab is the occurrence in tumors of truncated forms of both ErbB-1 and ErbB-2 that lack an extracellular domain. These truncated forms are therefore not recognized by antibodies to the usual external domains of these proteins. A truncated form of ErbB-2, termed p95, has greater kinase activity than wild-type ErbB-2. Lapatinib has been shown to inhibit baseline p95ErbB2 phosphorylation in BT474 cells and tumor xenografts, whereas trastuzumab neither binds to nor inhibits p95, suggesting that trastuzumab resistance may be mediated through expression of p95ErbB2 during disease progression [28]. Moreover, p95ErbB2 expression has been found to be an independent prognostic factor in breast cancer and defines a group of patients with ErbB-2–overexpressing breast cancer with significantly worse outcome in terms of inferior disease-free survival [29].

**LAPATINIB PRECLINICAL INVESTIGATIONS**

In vitro studies of lapatinib on ErbB-2–overexpressing breast cancer cell lines (BT474) show that lapatinib dramatically inhibits the phosphorylation of ErbB-1 and ErbB-2, and of Akt, in a dose-dependent manner. In a mouse BT474 xenograft model, lapatinib inhibited tumor growth by 94% [28]. The activation of mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3'-kinase (PI3K) signaling pathways is essential for cell cycle progression, and the TK inhibitors lapatinib and gefitinib inhibit these pathways in various malignancies [28]. Lapatinib inhibits both growth-factor–stimulated MAPK signaling and HER-2/neu–induced PI3K/Akt signaling, suggesting that this TK inhibitor is an effective cancer chemotherapeutic agent [28]. Lapatinib is a potent inhibitor of both the ErbB-1 (HER-1) and ErbB-2 (HER-2) tyrosine kinases, and it has shown significant anti-tumor activity in a variety of cancer models, including breast cancer, non-small cell lung cancer, and colorectal cancer [28]. Lapatinib has also shown to inhibit HER3, a component of the EGFR family, and it is currently being evaluated in combination with other agents in clinical trials [28].

**Figure 1.** Schematic outline of the epidermal growth factor receptor family and some dimerization possibilities [1, 5, 9, 20, 21].

**Figure 2.** The epidermal growth factor receptor cascade of events following ligand binding and tyrosine kinase receptor activation. Abbreviations: JNK, Jun N-terminal kinase; PI3K, phosphatidylinositol 3' kinase; PKC, protein kinase C; PLCγ, phospholipase C; MAPK, mitogen-activated protein kinase; MEK, MAPK/extracellular signal–related kinase (ERK) kinase; MEKK, MEK kinase; mTOR, mammalian target of rapamycin. Adapted from Atalay G, Cardoso F, Awada A et al. Novel therapeutic strategies targeting the epidermal growth factor receptor (EGFR) family and its downstream effectors in breast cancer. Ann Oncol 2003;14:1346–1363, with permission.

**Figure 3.** Lapatanib binds to the tyrosine kinase (TK) domain, competitively blocking ATP binding, thus inhibiting the downstream cascade of events.
protein kinase (MAPK) is also inhibited by lapatinib in preclinical models [28]. This indicates that Akt and MAPK may be useful biomarkers in determining the efficacy of lapatinib [28, 30].

Preclinical studies have also revealed synergistic cell growth inhibition with simultaneous targeting of EGFR and ErbB-2 receptor TKs. Lapatinib exhibits greater growth inhibition of colon cancer cells activated by the EGFR ligand transforming growth factor alpha than antagonists targeting either EGFR or ErbB-2 alone [6, 31]. Furthermore, lapatinib is able to suppress ErbB-1, ErbB-2, Akt, and MAPK in a concentration-dependent manner [31]. In vivo, lapatinib is also effective in blocking GEO human colon cancer cell xenograft growth [31].

Lapatinib demonstrates a potent inhibitory effect on ErbB-1 and ErbB-2 with a 50% inhibitory concentration (IC_{50}) <0.2 μM in several breast cancer cell lines and murine xenograft studies [6, 27, 30, 32]. Lapatinib inhibits ErbB-1 and ErbB-2 activation and inhibits cell proliferation in various breast cancer cell lines that overexpress either ErbB-1 or ErbB-2, and in a cell line resistant to trastuzumab [28, 30, 33]. Lapatinib produces a concentration-dependent antiproliferative effect in all breast cancer cell lines, with differences in the IC_{50} in individual cell lines [34]. There is a significant correlation between the response to lapatinib with ErbB-2 expression and its ability to inhibit ErbB-2, Raf, Akt, and ERK phosphorylation [34]. In cell lines selected for long-term outgrowth (>9 months) in a trastuzumab-containing (100 μg/ml) culture medium, lapatinib has significant in vitro activity [34].

In long-term (treatment over 77 days) in vivo studies with human breast cancer xenografts in athymic mice, lapatinib produces a significant and sustained reduction in xenograft volume versus untreated controls [34]. In murine mammary xenografts of estrogen receptor (ER)-positive, tamoxifen-resistant breast tumors, lapatinib is also able to restore tamoxifen sensitivity. The combination of lapatinib and tamoxifen leads to a more rapid and profound antiproliferative effect than with either of the drugs on their own [9]. A synergistic effect is observed with the combination of lapatinib and trastuzumab in four different ErbB-2-overexpressing cell lines [34].

The effect of lapatinib on radiosensitization has also been evaluated in breast cancer cell lines. Lapatinib has a radiosensitizing effect mediated through EGFR signaling, which may be useful in overcoming radioresistance [30, 33, 35].

These results from preclinical studies provided the biological rationale to evaluate lapatinib clinically, both as a single agent and in combination with tamoxifen or trastuzumab in breast cancer patients [9, 34].

**Phase I and Pharmacokinetic Clinical Trials with Lapatinib**

Phase I studies were developed to determine the feasibility and safety of lapatinib first in healthy human volunteers and then in patients with cancer (Table 1) [30, 36–53]. Lapatinib was well tolerated with no severe adverse events reported. The most common side effects reported included diarrhea, rash, nausea, vomiting, and headache. Burris and colleagues treated 64 heavily pretreated patients with solid tumors (EGF10003 study) with either a once-daily (qd) or twice-daily (bid) dose of lapatinib in a dose-escalation manner [6, 39, 40]. Lapatinib was well tolerated in this heavily pretreated patient population, with rash, diarrhea, nausea/vomiting, fatigue, and anorexia being the most frequent grade 1 or 2 adverse events in all cohorts [6, 40]. There were no grade 4 toxicities and a dose-limiting toxicity (DLT) was not observed, although grade 3 diarrhea was observed at the 900 mg bid dose level [6]. Of note, one patient with head and neck cancer had a complete response (CR) and 22 patients had stable disease (SD) (Table 1) [40].

A phase IB study evaluated lapatinib in heavily pretreated metastatic cancer patients whose tumors overexpressed ErbB-1 and/or ErbB-2 (EGF10004 study) [6, 42–45]. Lapatinib was well tolerated at doses up to 1,600 mg daily, with clinical activity observed at doses in the range of 650–1,600 mg daily. Four patients with trastuzumab-resistant metastatic breast cancer had a partial response (PR) and 22 patients with various other solid tumors achieved disease stabilization (Table 1) [44]. A DLT was not observed. Overall, the most frequent adverse events were diarrhea and rash [44]. There were no grade 4 drug-related adverse events, pneumonitis, or cardiac dysfunction [44]. Frequency of diarrhea was linearly related to dose but not to serum concentration of drug, suggesting that this toxicity evolves from a local effect on the gut epithelium.

Numerous phase I combination trials have been conducted and are summarized in Table 1 [6, 30, 36–53]. The single-agent phase I trials demonstrate that lapatinib is well tolerated with clinical responses in various solid tumors reported. It was based on these results that phase II trials were initiated.

**Lapatinib in the Treatment of Breast Cancer**

Several efficacy trials have been conducted in patients with advanced or metastatic disease. Phase II and III clinical trials conducted to date for the treatment of refractory and first-line metastatic breast cancer and in the adjuvant setting are summarized in Table 2 [6, 54–61]. (Of note, the dosing of lapatinib in combination or as a single agent differs among these clinical trials.)
There have been two phase II trials of single-agent lapatinib in patients with refractory metastatic breast cancer [55–58]. In the EGF20002 study, 78 patients with ErbB-2–overexpressing metastatic breast cancer, with progressive disease on prior trastuzumab-containing regimens, received lapatinib daily at a dose of 1,500 mg [55–57]. In the EGF20008 study, metastatic breast cancer patients who developed progressive disease following prior treatment with anthracyclines, taxanes, and capecitabine (Xeloda®; Roche Laboratories Inc., Nutley, NJ) received 1,500 mg/day lapatinib and were divided into cohort A (n = 140) and cohort B (n = 89).

### Table 1. Overview of the phase I clinical trials with lapatinib

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor</th>
<th>Lapatinib dose (mg)</th>
<th>n of patients</th>
<th>Response (n)</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy, healthy volunteers</strong></td>
<td></td>
<td></td>
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<tr>
<td>DeSimone et al. [36]; Bence et al. [37];</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10–250&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bence et al. [37]; Adams et al. [38]</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25–175&lt;sup&gt;c&lt;/sup&gt;</td>
<td>27&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Monotherapy, second line</strong></td>
<td></td>
<td></td>
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<tr>
<td>Burris et al. [6, 39]; Versola et al. [40]; Pandite et al. [41]; EGF10003</td>
<td>Solid tumors</td>
<td>175–1,800 qd 500, 750, 900 bid</td>
<td>39</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>EGF1004 [40, 42–45]</td>
<td>Solid tumors</td>
<td>500–1,600 qd</td>
<td>67</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>Minami et al. [46]</td>
<td>Solid tumors</td>
<td>900–1,800 qd</td>
<td>Cohorts of 6</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td><strong>Combination therapy, second line</strong></td>
<td></td>
<td></td>
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<tr>
<td>De Bono et al. [47]</td>
<td>Solid tumors</td>
<td>L, 1,250 qd&lt;sup&gt;d&lt;/sup&gt;, plus C, 1,500 mg/m²/day bid&lt;sup&gt;d&lt;/sup&gt;</td>
<td>11</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Chu et al. [48]</td>
<td>Breast, ovarian, endometrial</td>
<td>L, 1,250–1,500 qd, plus letrozole, 2.5 mg/day</td>
<td>36</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Lakhai et al. [49]</td>
<td>Solid tumors</td>
<td>L, 1,250–1,500 qd, plus FOLFOX&lt;sup&gt;e&lt;/sup&gt; −20% std dose to std dose</td>
<td>13</td>
<td>–</td>
<td>2/7</td>
</tr>
<tr>
<td>Jones et al. [50]; EGF10009</td>
<td>Solid tumors</td>
<td>L, 1,250–1,500 qd, plus P, 135–225 mg/m² q3w</td>
<td>26</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Midgley et al. [51]</td>
<td>Solid tumors</td>
<td>L, 1,000 or 1,250 qd, plus FOLFIRI q14d 80% or 60% std dose</td>
<td>25</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>Storniolo et al. [52]</td>
<td>MBC</td>
<td>L, 750–1,500 qd, plus T, 4 mg/kg&lt;sub&gt;bolus&lt;/sub&gt; →wkly 2 mg/kg&lt;sub&gt;inf&lt;/sub&gt;</td>
<td>48</td>
<td>1/27</td>
<td>5/27</td>
</tr>
<tr>
<td>Safran et al. [53]</td>
<td>Pancreaticobiliary cancers</td>
<td>L, 1,000 or 1,500 qd, plus weekly gemcitabine or GEMOX&lt;sup&gt;e&lt;/sup&gt;</td>
<td>21</td>
<td>5/20 responded</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup>Healthy volunteers; <sup>b</sup>Single dose; <sup>c</sup>Multiple dose; <sup>d</sup>Initial dose. Abbreviations: bid, twice daily; C, capecitabine; CR, complete response; D1&2, days 1 and 2; DLT, dose-limiting toxicity; FOLFOX, oxaliplatin (OX)/5-fluorouracil (5-FU), and leucovorin (LV); GEMOX, gemcitabine 1 g/m² over 100 minutes and oxaliplatin 100 mg/m², every 14 days; inf, infusion; L, lapatinib; MBC, metastatic breast cancer; NA, not applicable; NR, not reported; OTR, optimally tolerated regimen; P, paclitaxel; PR, partial response; q3w, every 3 weeks; q14d, every 14 days; qd, once daily; RD, recommended dose; SD, stable disease; std, standard; T, trastuzumab.

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**Refractory Metastatic Breast Cancer**

There have been two phase II trials of single-agent lapatinib in patients with refractory metastatic breast cancer [55–58]. In the EGF20002 study, 78 patients with ErbB-2–overexpressing metastatic breast cancer, with progressive disease on prior trastuzumab-containing regimens, received lapatinib daily at a dose of 1,500 mg [55–57]. In the EGF20008 study, metastatic breast cancer patients who developed progressive disease following prior treatment with anthracyclines, taxanes, and capecitabine (Xeloda®; Roche Laboratories Inc., Nutley, NJ) received 1,500 mg/day lapatinib and were divided into cohort A (n = 140) and cohort B (n = 89).
Cohort A included ErbB-2–overexpressing trastuzumab-refractory metastatic breast cancer patients, while cohort B included ErbB-2–nonoverexpressing metastatic breast cancer with no prior trastuzumab [57, 58]. In the preliminary analysis, the clinical benefit rate (CBR = CR + PR + SD) was 22% of patients in the EGF20002 study and 14% of patients in the EGF20008 study (Table 2) [55–58]. A combined biomarker analysis was also conducted for these two studies, to determine the relevant tissue and serum biomarkers that would predict the response to single-agent lapatinib. Tumors were stained by immunohistochemistry (IHC) for ErbB-1 to ErbB-4, insulin-like growth factor 1 (IGF-1), and IGF-1 receptor, as well as for Ki-67. The expression of these markers was correlated with the clinical response to lapatinib.

### Table 2. Overview of the phase II and III clinical trials with lapatinib

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Phase</th>
<th>Primary end points</th>
<th>Study</th>
<th>Treatment</th>
<th>Phase</th>
<th>Primary end points</th>
<th>Response (%)</th>
<th>TTP (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory metastatic breast cancer patients</td>
<td>EGF20002 [54–56]</td>
<td>Lapatinib</td>
<td>II</td>
<td>RR, safety</td>
<td>Cohort A</td>
<td>Capecitabine + lapatinib vs. capecitabine</td>
<td>III</td>
<td>OS, TTP, RR</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>EGF20008 [54, 57]</td>
<td>Lapatinib</td>
<td>II</td>
<td>RR, safety</td>
<td>Cohort B</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EGF100151 [58]</td>
<td>Capecitabine + lapatinib vs. capecitabine</td>
<td>III</td>
<td>OS, TTP, RR</td>
<td>EGF104900 [59]</td>
<td>Trastuzumab + lapatinib vs. lapatinib</td>
<td>III</td>
<td>PFS, RR</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>EGF105058 [59]</td>
<td>Lapatinib in brain metastases</td>
<td>II</td>
<td>RR</td>
<td>NCI-CTEP 6969 trial [66]</td>
<td>Lapatinib in brain metastases</td>
<td>II</td>
<td>RR in CNS</td>
<td>13%</td>
</tr>
<tr>
<td>First-line advanced breast cancer patients</td>
<td>EGF20009 [68, 69]</td>
<td>Lapatinib qd vs. bid</td>
<td>II</td>
<td>RR</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>EGF30001 [60]</td>
<td>Paclitaxel + lapatinib vs. paclitaxel + placebo</td>
<td>III</td>
<td>TTP, OS, RR, biomarker</td>
<td></td>
<td></td>
<td></td>
<td>In progress</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EGF30008 [53, 60]</td>
<td>Letrozole + lapatinib vs. letrozole + placebo</td>
<td>III</td>
<td>TTP, OS, RR, biomarker</td>
<td></td>
<td></td>
<td></td>
<td>In progress</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EGF104383 [60]</td>
<td>Paclitaxel + trastuzumab + lapatinib vs. paclitaxel + trastuzumab + placebo</td>
<td>III</td>
<td>TTP, OS, RR, biomarker</td>
<td></td>
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<td></td>
<td>In progress</td>
<td></td>
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<tr>
<td></td>
<td>EGF104353 [60]</td>
<td>Paclitaxel + lapatinib vs. paclitaxel + placebo</td>
<td>III</td>
<td>TTP, OS, RR, biomarker</td>
<td></td>
<td></td>
<td></td>
<td>In progress</td>
<td></td>
</tr>
<tr>
<td>Inflammatory breast cancer (IBC) patients</td>
<td>EGF103900 [60, 80]</td>
<td>Lapatinib in refractory IBC</td>
<td>II</td>
<td>RR</td>
<td>Cohort A</td>
<td>Lapatinib</td>
<td>II</td>
<td>NR</td>
<td>In progress</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cohort B</td>
<td>Lapatinib</td>
<td>II</td>
<td>NR</td>
<td>In progress</td>
</tr>
<tr>
<td>Adjuvant breast cancer patients</td>
<td>GSK + BIG [60]</td>
<td>Trastuzumab (1 yr) vs. lapatinib (1 yr) vs. trastuzumab + lapatinib (1 yr) vs. lapatinib (6 mo) vs. trastuzumab (6 mo)</td>
<td>III</td>
<td>OS, TTP, RR, safety</td>
<td></td>
<td></td>
<td></td>
<td>In progress</td>
<td></td>
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<tr>
<td></td>
<td>TEACH</td>
<td>Lapatinib (1 yr) vs. placebo</td>
<td>III</td>
<td>DFS, OS, CNS recurrence, QOL</td>
<td></td>
<td></td>
<td></td>
<td>In progress</td>
<td></td>
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</tbody>
</table>

*Investigator-reported preliminary data.
*16-week progression free + responders.
*Best non-CNS response in 4/16 patients with measurable disease.

Abbreviations: bid, twice daily; BIG, Breast Cancer International Group; CNS, central nervous system; CR, complete response; DFS, disease-free survival; GSK, GlaxoSmithKline; NCI-CTEP, National Cancer Institute Cancer Therapy Evaluation Program; NR, not reported; OS, overall survival; PFS, progression-free survival; PR, partial response; qd, once daily; QOL, quality of life; RR, response rate; SD, stable disease; TEACH, Tykerb® Evaluation After Chemotherapy; TTP, time to progression.
receptor (IGF1R), truncated ErbB-2 (p95), heregulin, and p-ERK-1/2 [55]. The initial data showed that metastatic breast cancer patients were more likely to respond to lapatinib if their disease was ER negative, progesterone receptor (PgR) negative, and ErbB-2 overexpressing [55]. Furthermore, a decline in serum ErbB-2 extracellular domain after 4 and 8 weeks of lapatinib therapy correlated with clinical response [55].

A phase I trial of lapatinib in combination with capecitabine demonstrated a well-tolerated safety profile and evidence of clinical activity [47]. Thus, a phase III trial (EGF100151 study) comparing lapatinib in combination with capecitabine with capecitabine alone was conducted in ErbB-2–positive or locally advanced breast cancer patients who had developed progressive disease following prior treatment with anthracyclines, taxanes, and trastuzumab [59]. Patients were randomly assigned to receive either oral lapatinib (1,250 mg qd continuously) in combination with oral capecitabine (2,000 mg/m² per day on days 1–14) (n = 160) or the widely accepted third-line regimen capecitabine monotherapy (2,500 mg/m² per day on days 1–14) (n = 161) every 3 weeks [59]. The primary end point was time to progression (TTP), and secondary end points were overall survival, progression-free survival, response rate, CBR, and toxicity. The groups were well balanced in terms of patient characteristics and disease characteristics. In both groups, >97% of patients had received prior therapy with anthracyclines, >98% had also received taxanes, and 97% of patients had received prior trastuzumab. In the lapatinib plus capecitabine arm, the median TTP was 37 weeks, versus 20 weeks in the capecitabine alone arm (p = .00016) (Table 2). Similarly, in the combination arm, the median progression-free survival time was 37 weeks, compared with 18 weeks for those in the capecitabine monotherapy arm (p = .000045). The overall response rate was 23% in the combination therapy group and 14% in the capecitabine monotherapy group (p = .113) in the independent intent-to-treat analysis. At the time of writing of this manuscript, the median overall survival duration had not yet been reached. In terms of toxicities, the rates of adverse events were similar in the two arms both in terms of overall events and serious adverse events. Fourteen percent of patients in the lapatinib plus capecitabine group versus 11% of patients in the capecitabine alone group required discontinuation of therapy as a result of adverse events. The most common included diarrhea (58% versus 39%), hand–foot syndrome (43% versus 34%), and rash and/or skin reaction (35% versus 30%) (all grades, for lapatinib plus capecitabine versus capecitabine alone, respectively). In the combination arm, four patients experienced cardiac events that were treatment related and all fully recovered, while one patient in the capecitabine monotherapy group experienced a cardiac event unrelated to treatment that remained unresolved.

In summary, the combination of lapatinib and capecitabine produced a significantly longer median TTP in ErbB-2–positive refractory metastatic breast cancer patients compared with capecitabine alone, with a well-tolerated safety profile. Declines in left ventricular ejection fraction (LVEF) were infrequent, asymptomatic, and reversible [59]. Furthermore, fewer patients in the combination group developed brain relapses compared with those in the single-agent capecitabine group (4 patients versus 11 patients; p = .110).

Another phase III trial is ongoing comparing lapatinib in combination with trastuzumab with trastuzumab alone in 270 patients with ErbB-2–overexpressing metastatic breast cancer who developed progressive disease on prior trastuzumab therapy (Table 2). The results are awaited with interest.

**Brain Metastases**

Patients with ErbB-2–overexpressing breast cancer have been found to have a significantly higher risk for developing brain metastases [62]. Several studies have also found a higher incidence of brain metastases in patients treated with trastuzumab, further supporting the hypothesis that ErbB-2–overexpressing breast cancer may have a predilection for metastasizing to the brain [63, 64]. Stemmler and colleagues have investigated why ErbB-2–overexpressing metastatic breast cancer patients receiving trastuzumab suffer from an increased risk for developing brain metastases, even though visceral disease might be responsive to trastuzumab, and had failed local therapy [65, 66]. They found that while trastuzumab was effective in treating liver and lung metastases, approximately one third of ErbB-2–overexpressing metastatic breast cancer patients develop brain metastases. This observation suggests that the blood–brain barrier prevents trastuzumab from reaching adequate concentrations in the central nervous system (CNS) [65, 66]. Therefore, clinical trials have been carried out with lapatinib for the treatment of brain metastases because it is a small molecule able to penetrate the blood–brain barrier.

Results from a phase II trial with lapatinib for ErbB-2–overexpressing breast cancer patients with new or progressive brain metastases were presented at the 2006 American Society of Clinical Oncology (ASCO) Annual Meeting [67]. In that study, patients received oral lapatinib at a dose of 750 mg twice daily. The primary end point was objective response in the central nervous system. Thirty-nine patients who had developed CNS disease during treatment with trastuzumab were enrolled. There were no grade 4
toxicities among the 39 patients. The most common grade 3 adverse events included diarrhea (21%), fatigue (15%), headache (10%), and rash (5%). There were no cases of grade 3 or 4 cardiac dysfunction, while 4 of the 39 patients developed asymptomatic grade 2 LVEF <50%. By the Response Evaluation Criteria in Solid Tumors (RECIST), two patients (5%) had a PR as the best CNS response and 4 of 16 patients (25%) with measurable disease had a PR as the best non-CNS response [67]. Eight patients had SD in the CNS at 16 weeks. The volumetric analysis, a three-dimensional measure of tumor size, showed more promising results than the results as measured by RECIST. The median TTP was 3.02 months (95% confidence interval, 2.04–3.68 months) and the overall survival time was 6.57 months. Lapatinib was well tolerated in this patient population and there was some evidence of CNS clinical activity [67].

First-Line Metastatic Breast Cancer Trials

Phase I and II clinical trials showed that lapatinib is an active agent in the treatment of refractory metastatic breast cancer and has manageable toxicity. Thus, studies were conducted with lapatinib as a first-line treatment for patients with locally advanced or metastatic breast cancer.

In the EGF20009 study, locally advanced or metastatic breast cancer patients with ErbB-2 amplification (as documented by fluorescence in situ hybridization [FISH]) were randomized to receive lapatinib at a dose of either 1,500 mg qd or 500 mg bid [68, 69]. Eligible patients had not received prior trastuzumab for metastatic disease. The primary end point was response rate. The planned number of patients was 130. An interim analysis is available on 40 patients, 19 on the 500 mg bid schedule and 21 on the 1,500 mg qd schedule. Twenty-five percent of patients had stage IIIB or IIC disease, and 75% had stage IV disease. There were no reported grade 3 or 4 adverse events and no unexpected toxicities. By independent radiology review, 35% of the patients had a PR and a further 5% had unconfirmed PRs; 35% of the patients had SD, 12.5% had progressive disease, and 12.5% were not evaluable (Table 2) [68, 69].

Several phase III trials with lapatinib as part of combination first-line therapy are also ongoing in patients with advanced breast cancer (Table 2). Based on the activity observed with lapatinib in combination with paclitaxel (Taxol®; Bristol Myers Squibb Company, Princeton, NJ) and also with trastuzumab in phase I studies, the combinations selected for use in the phase III trials include: lapatinib plus paclitaxel versus paclitaxel plus placebo; paclitaxel plus trastuzumab plus lapatinib versus paclitaxel plus trastuzumab plus placebo; and paclitaxel plus lapatinib versus paclitaxel plus placebo [50, 52, 61].

In hormone receptor–positive breast cancer, endocrine therapy is widely accepted as the standard of care. However, estrogen depletion upregulates ErbB-2, and an increase in serum level of ErbB-2 has been associated with endocrine therapy resistance [61, 70–77]. Preclinical studies showed promising results with combinations of endocrine therapy with ErbB-1/ErbB-2 inhibitors, and the preclinical data also revealed that lapatinib may overcome hormonal resistance [9, 54, 74, 75]. As letrozole (Femara®; Novartis Pharmaceuticals Corporation, East Hanover, NJ) is well tolerated as an adjuvant therapy, and the phase I combination study with lapatinib and letrozole showed clinical benefit, a phase III trial of letrozole plus lapatinib versus letrozole plus placebo, in 1,280 postmenopausal patients with ER-positive first-line metastatic breast cancer, regardless of ErbB-2 status, was initiated (Table 2) [48, 78–80].

Inflammatory Breast Cancer Studies

Data from the small number of inflammatory breast cancer (IBC) patients involved in the phase I studies of lapatinib indicated that lapatinib may be effective in this subset of patients [81]. Moreover, IBC has a higher prevalence of ErbB-2 overexpression than non-IBC locally advanced breast cancer [82]. These provided a rationale for clinical investigation of lapatinib in IBC. Spector and colleagues presented preliminary results at the 2006 ASCO Annual Meeting on the EGF103009 study, a phase II multicenter trial of single-agent lapatinib for the treatment of relapsed or refractory IBC [81]. Initial results were presented on 36 patients who were assigned to cohort A (ErbB-2 overexpressors, defined as a score of 2 or 3+ on IHC or positive by FISH; n = 24) or cohort B (ErbB-1 and/or ErbB-2 nonoverexpressors) and received 1,500 mg/day lapatinib [81]. A 62% PR rate was seen in ErbB-2–positive patients in cohort A, 21% had SD, giving a CBR of 83% (Table 2) [60, 81]. In cohort B, 8.3% of patients had a PR, 17% had SD, and 17% are still pending analysis [60, 81].

To further investigate the efficacy of lapatinib in IBC, a phase II trial is ongoing with lapatinib in combination with paclitaxel for neoadjuvant therapy of IBC (Table 2). Lapatinib is a promising anticancer therapy for patients with IBC.

Adjuvant Breast Cancer Trials

Lapatinib is potentially an ideal therapy for the adjuvant treatment of breast cancer, because it has shown activity in the first-line and refractory metastatic settings, it appears to have a low incidence of cardiotoxicity, it may decrease the incidence of later brain metastases, and it offers convenience of use (oral, qd administration) [61]. Several investigators are currently considering clinical investigations of lapatinib in early-stage ErbB-2–overexpressing breast cancer.
A cooperative group multi-arm adjuvant trial with lapatinib as the experimental drug in approximately 8,000 patients is planned to start enrolling patients in 2006 (Table 2) [61].

We have initiated a phase III randomized, double-blind, multicenter, placebo-controlled trial of lapatinib in the adjuvant setting, called the TEACH (Tykerb® Evaluation After Chemotherapy) trial, that is currently enrolling patients. The objective of the TEACH trial is to determine whether adjuvant therapy with lapatinib for 1 year will improve disease-free survival in women with early-stage ErbB-2–overexpressing breast cancer. Eligible women must have completed adjuvant chemotherapy, be free of disease, and have either a new diagnosis and be unable or unwilling to receive trastuzumab or have a remote diagnosis of ErbB-2–overexpressing breast cancer and not have received prior trastuzumab. Three thousand women will be enrolled, with 32 countries participating in this study. Disease-free survival will be compared in women treated with lapatinib versus placebo, as well as overall survival, recurrence-free interval, rate of CNS recurrence, toxicity, and quality of life (Fig. 4). This trial will help to determine the effectiveness of lapatinib in early-stage breast cancer given both as immediate and delayed therapy in ErbB-2–positive disease. Centralized pathology will be reviewed and all patients will be asked for permission to bank tumors for correlative science studies.

**Cardiac Toxicity**

Cardiac toxicity was an unexpected finding in the pivotal phase III trial of trastuzumab, the monoclonal antibody of ErbB-2 [83]. Most women with ErbB-2–overexpressing breast cancer have usually received both anthracyclines and trastuzumab, thereby receiving two potentially cardiotoxic drugs. Among metastatic breast cancer patients on trastuzumab, about 11% experience grade 3 cardiac toxicity, but most cardiac symptoms improve with discontinuation of trastuzumab and initiation of appropriate cardiac medical therapy [84]. The most recent results of the adjuvant clinical trials of trastuzumab following anthracycline-containing therapy have reported that the risk for severe congestive heart failure (CHF) is approximately 2%–4% [85, 86].

Because of the associated cardiac toxicity observed with trastuzumab, Perez and colleagues analyzed cardiac function in patients treated with lapatinib in 18 phase I–III lapatinib clinical trials [83, 85, 87, 88]. Ten of the trials involved lapatinib as monotherapy and eight included lapatinib in combination with capecitabine, letrozole, paclitaxel, cisplatin, or oxaliplatin/5-fluorouracil. There were 3,127 patients who had received lapatinib included in this analysis, including 1,674 breast cancer patients (596 monotherapy and 1,078 combination therapy) and 1,453 patients with other cancers (i.e., colorectal cancer, non-small cell lung cancer, renal cancer, head and neck cancer, scrotal sarcoma, urothelial carcinoma) [85]. In the cardiac safety evaluation, only 1.3% of patients (41/3,127) receiving lapatinib experienced a decrease in LVEF, which was mostly asymptomatic (i.e., 1.2% asymptomatic and 0.1% symptomatic). However, in contrast to the breast cancer trials, a substantial number of participants in the non–breast cancer trials had not received prior anthracycline therapy or trastuzumab and this could partially explain the low incidence of cardiac failure in this analysis. However, LVEF was similarly affected by lapatinib in both the breast cancer and non–breast cancer patients. Time to onset of an LVEF decrease was within 9 weeks of treatment in 66% of patients, 10–16 weeks in 15% of patients, and 17–24 weeks in 12% of patients. The 0.1% of symptomatic patients with decreased LVEF presented with dyspnea, palpitations, and signs of CHF. However, they responded promptly to standard cardiac management. The 1.3% incidence of symptomatic and asymptomatic decreases in LVEF in patients treated with lapatinib was less than that expected within a matched cohort of the gen-

**Figure 4.** Tykerb® Evaluation After Chemotherapy (TEACH) trial study schema. Eligible patients must have received adjuvant chemotherapy. Accrual goal = 3,000 patients. Abbreviations: ER, estrogen receptor; NED, no evidence of disease; PgR, progesterone receptor; qd, once daily.
eral population (3%−6% incidence of asymptomatic LVEF decrease) and less than that of trastuzumab-treated breast cancer patients [85, 89]. Thus, there is currently no firm evidence that lapatinib causes cardiac toxicity at all. These cardiac safety results further support the rationale for studying lapatinib in the adjuvant setting.

**Conclusions**

In conclusion, lapatinib is an active and well-tolerated oral dual TK inhibitor for the treatment of breast cancer. Clinical efficacy of lapatinib is limited only to the treatment of ErbB-2−overexpressing breast cancer. Lapatinib is active in refractory metastatic breast cancer patients and as a first-line metastatic treatment, with potential benefit in patients with brain metastases. Importantly, lapatinib has demonstrated efficacy in combination with capecitabine in patients with refractory ErbB-2−overexpressing breast cancer. Lapatinib appears to have either very low or no incidence of cardiotoxicity. The most frequently reported adverse events include nausea, fatigue, itching, rash, diarrhea, acne, and dry skin. However, grade 3 and 4 toxicities are rare, and most adverse events associated with lapatinib are of grade 1 or 2 in severity.

Our improved understanding of the biology of breast cancer and the use of biomarkers for identification of specific subtypes of breast cancer allows us to bring patient-specific novel therapies such as lapatinib to the clinic [55, 90]. Results from the phase III trials with lapatinib in combination regimens and from the adjuvant trials are eagerly awaited.

**Disclosure of Potential Conflicts of Interest**

B.M. has acted as a consultant for Genentech.

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