Lapatinib: new opportunities for management of breast cancer

Julia Liao 1
Michelle Gallas 1
Mark Pegram 1,2,3
Joyce Slingerland 1,2,3,4
1Braman Family Breast Cancer Institute, 2Division of Hematology/Oncology, University of Miami Sylvester Comprehensive Cancer Center, 3Departments of Medicine, 4Biochemistry and Molecular Biology, University of Miami Miller School of Medicine, Miami, FL, USA

Abstract: Approximately 20% of new diagnosed breast cancers overexpress the human epidermal growth factor receptor 2 (EGFR2), also known as erythroblastic leukemia viral oncogene homolog 2 (ERBB2) protein, as a consequence of ERBB2 gene amplification, resulting in a poor prognosis. Clinical outcome can be substantially improved by ERBB2-targeted therapy. Lapatinib is a potent, orally bioavailable small molecule that reversibly and selectively inhibits epidermal growth factor receptor (EGFR1 or ERBB1) and ERBB2 tyrosine kinases. Lapatinib binds the adenosine triphosphate-binding site of the receptor’s intracellular domain to inhibit tumor cell growth. This review summarizes the pharmacology, pharmacokinetics, efficacy, and tolerability of lapatinib, and reviews both Food and Drug Administration-approved and investigational uses of lapatinib in breast cancer therapy. The drug is generally well tolerated in patients, with diarrhea and rashes being the most common (usually mild or moderate) adverse effects. Unlike trastuzumab, lapatinib has infrequent adverse effects on cardiac function. Lapatinib has substantial activity for advanced ERBB2-positive breast cancer, particularly in combination with capecitabine, following progression after anthracyclines, taxanes, and trastuzumab. Lapatinib combined with capecitabine yielded significant improvements in time to progression and response rate compared with capecitabine alone. This drug can also be combined with letrozole for the treatment of postmenopausal women with ERBB2-positive breast cancer, for whom hormonal therapy is indicated. Lapatinib has shown early promise in treatment of central nervous system metastasis and is being further evaluated in various clinical settings.

Keywords: lapatinib, trastuzumab, ERBB family, ERBB2, breast cancer, capecitabine, letrozole

Introduction
Breast cancer is the second leading cause of cancer death amongst women in the US, and the most common form of cancer in women. In 2009, an estimated 194,280 new cases and 40,610 deaths resulted from breast cancer.1 As our knowledge and understanding of tumor cell biology has increased, adjuvant therapy has resulted in consistent incremental improvements in clinical outcome over the past decade. Despite these encouraging results in treating early breast cancer, the treatment of metastatic disease continues to pose formidable challenges. With metastatic breast cancer accounting for over 40,000 deaths each year in the US, novel therapeutic approaches to this pressing challenge are needed.1

Cancer is almost invariably linked to abnormal molecular circuitry, involving signaling pathways that control cell growth and differentiation. One crucial pathway that plays a central role in oncologic signaling in breast and certain other cancers begins
with ERBB receptors, also known as epidermal growth factor receptors (EGFR). The ERBB family of receptor tyrosine kinases consists of four homologous members, i.e., ERBB1 (EGFR, HER1), ERBB2 (HER2, c-ERBB2, neu), ERBB3 (HER3), and ERBB4 (HER4). ERBB receptors are crucial in organ development and regulating cellular differentiation and morphogenesis in a broad variety of tissues. ERBB1 and ERBB2 have been shown to promote the growth and survival of various types of epithelial malignancies. ERBB1 is overexpressed in up to 30% of human breast cancers, and ERBB2 is amplified and overexpressed in up to 20% of primary human breast cancers.\(^2\)\(^-\)\(^5\) ERBB1 overexpression has been documented in up to 60% of nonsmall cell lung cancer tumors.\(^6\)\(^-\)\(^8\) ERBB3 has been implicated in the pathogenesis of multiple tumor types, including breast and ovarian cancers, while the ERBB4 gene is mutated in approximately 20% of melanomas.\(^10\)\(^,\)\(^11\)

ERBB receptors are composed of an extracellular ligand-binding domain, a single transmembrane domain, and an intracellular tyrosine kinase domain. ERBB receptors exist in a predimerized state.\(^12\) When ligands such as epidermal growth factor, transforming growth factor-\(\alpha\), amphiregulin, epieregulin, and heregulin bind to the predimerized state, a 2:2 ligand-to-receptor configuration is formed by the rotation of the transmembrane domain and subsequent rearrangement of each receptor subunit.\(^13\) Ligand binding to the extracellular domain ignites conformational rearrangements, triggering receptor dimerization to form ERBB homodimers and heterodimers that result in the recruitment and promotion of downstream signal transduction. The two best studied signaling pathways activated by this signaling cascade are the mitogen-activated protein kinase and the best studied signaling pathways activated by the signaling and promotion of downstream signal transduction. The two best studied signaling pathways activated by this signaling cascade are the mitogen-activated protein kinase and the phosphatidylinositol 3-kinase (PI3K) pathways. The many tyrosine phosphorylation sites of ERBB3 serve as potent modules to activate intracellular signaling, especially the PI3K pathway.\(^14\) Amplification and/or mutation of the ERBB receptors results in the deregulation of downstream effector pathways contributing to the pathogenesis of many human malignancies.\(^15\)

Members of the ERBB family, particularly ERBB1 and ERBB2, are commonly overexpressed, leading to deregulated proliferation and development, and contributing to oncogenesis in breast cancer. Immunohistochemical (IHC) studies have shown ERBB1 overexpression in up to 30% of primary breast cancers.\(^3\)\(^,\)\(^4\) This is germane to the understanding of ERBB2-targeted therapies, because ERBB1 can heterodimerize with ERBB2. It is unclear what proportion of new breast cancers co-overexpress both ERBB1 and ERBB2 together. Up to 20% of newly diagnosed breast cancers overexpress the ERBB2 gene due to gene amplification.\(^1\) When amplified, the ERBB2 gene leads to overexpression of p185\(^{\text{ERBB2}}\), a 185 kDa transmembrane glycoprotein and a well studied member of the ERBB family of receptor tyrosine kinases. ERBB2 amplification confers a particularly aggressive phenotype and poor prognosis, and therefore has been a prime target for the development of new breast cancer therapies. ERBB2 is the preferred binding partner for other ERBB receptor family members. Amplification of ERBB2 and resulting overexpression of the protein promotes spontaneous ligand-independent activation of the receptor’s kinase domain.

ERBB2 overexpression status is routinely evaluated in pathologic breast cancer specimens. IHC is an immunostaining method whereby an antibody is targeted to ERBB2 expressed by tumor cells. The current guidelines for ERBB2 status are summarized as follows. A tumor is identified as having ERBB2 amplification (being ERBB2-positive) either by showing uniform intense membrane staining in >30% of invasive tumor cells on IHC (scored as 3+ cell surface protein expression) or by a fluorescence in situ hybridization (FISH) result showing an amplified ERBB2 gene (average of >six gene copies/nucleus for test systems without an internal control probe) or an ERBB2/CEP17 ratio of more than 2.2, where CEP17 is a centromeric probe for chromosome 17 on which the ERBB2 gene resides. The false positive rate for ERBB2 scored as IHC 3+ (eg, that are actually not amplified) is small (<4%) and it is currently standard of care to accept a 3+ IHC as amplified without further testing.\(^16\)\(^-\)\(^18\) Patients are classified as having ERBB2-positive breast cancer based on positive results from either test. A negative ERBB2 test is defined as either an IHC result of 0 or 1+ for cellular membrane protein expression (no staining or weak, incomplete membrane staining in any proportion of tumor cells), or a FISH result showing an ERBB2/CEP17 ratio of less than 1.8 or an average of fewer than four copies of the ERBB2 gene per nucleus for systems without an internal control probe. IHC for ERBB-2 scored as 2+ requires further validation by FISH.

**Anti-ERBB2 therapies for breast cancer**

A number of new anticancer therapies have been developed to target breast cancers exhibiting ERBB2 amplification. The most important ERBB2-targeted therapies to date include monoclonal antibodies, antibody–drug conjugates, heat-shock protein-90 inhibitors, and tyrosine kinase inhibitors.\(^19\) Monoclonal antibodies function by binding to
the extracellular domain of the receptor, recruiting cytotoxic lymphocytes and perturbing ERBB2-mediated signaling events to result in cell cycle arrest in G₁. The first monoclonal antibody to be clinically developed was trastuzumab (Herceptin®; Genentech, Inc., San Francisco, CA).

These new classes of drugs targeting overexpressed ERBB2 have shown promising results in patients with ERBB2-positive breast cancers. Trastuzumab, a humanized monoclonal antibody that was approved by the US Food and Drug Administration (FDA) in 1998, is considered the backbone treatment for ERBB2-positive breast cancer. Trastuzumab’s high specificity and affinity for the extracellular domain IV of the ERBB2 receptor has been shown to benefit patients with ERBB2-positive metastatic breast cancer when administered alone or in combination with chemotherapy, promoting tumor regression and increasing time to tumor progression and overall survival.

Trastuzumab has also demonstrated significant activity in the adjuvant setting as a treatment for early ERBB2-positive breast cancer. Although the exact mechanism of action remains unknown, many have been proposed. Such mechanisms include inhibition of pathways involved in cell cycle progression, proteolytic cleavage of the ERBB2 receptor, inhibition of tumor angiogenesis and of DNA damage repair pathways, as well as of antibody-dependent cellular cytotoxicity.

The use of trastuzumab has become the standard of care for ERBB2-positive breast cancers in both the adjuvant setting and for metastatic breast cancers, but despite its benefits, a number of problems limit its clinical efficacy. Drug resistance, lack of penetration by trastuzumab of the blood–brain barrier with emergence of central nervous system metastasis, and cardiotoxicity are central among the limitations of trastuzumab in the clinical setting. Moreover, the need to administer trastuzumab intravenously adds to the cost and inconvenience of drug delivery. Both de novo and acquired resistance to trastuzumab have been observed. Most metastatic disease will progress within one year of beginning treatment, and recurrence has been observed with early breast cancer following adjuvant trastuzumab therapy.

Although effective in inhibiting metastasis to the liver, lymph nodes, and bone, trastuzumab is associated with an increase in risk of central nervous system metastasis as a site of first tumor recurrence. Finally, incidences of cardiotoxicity had been observed in the pivotal Phase III trial evaluating trastuzumab in combination with chemotherapy. Cardiac dysfunction was identified in 27% of ERBB2-positive patients treated with trastuzumab, an anthracycline, and cyclophosphamide, and in 13% of those treated with paclitaxel and trastuzumab. These results have led to stringent monitoring of left ventricular ejection fraction in all patients on trastuzumab regimens. Therefore, there is a need for new agents that are more efficacious and better tolerated to target the ERBB2 family of receptors.

A new generation of trastuzumab-based drugs is currently in clinical trials. These antibody–drug conjugates, such as trastuzumab-DM1 (Genentech, Inc.) are a novel category of anti-ERBB2 therapeutics. T-DM1 consists of trastuzumab conjugated to DM1, a derivative of the antimicrotubule agent, maytansine. The trastuzumab domain directs the drug to ERBB2 where DM1 is then internalized to exert its cytotoxic effects.

Pertuzumab is a monoclonal anti-ERBB2 antibody directed toward an epitope distinct from that targeted by trastuzumab, which interferes with receptor homo- and heterodimerization. It showed considerable efficacy in preclinical studies and good tolerability, bioavailability, and clinical activity upon three-weekly intravenous administration. While early clinical trials yielded disappointing results for pertuzumab in treatment of ERBB2-negative metastatic breast cancer, it may have a role together with trastuzumab in the treatment of trastuzumab-refractory, ERBB2-positive breast cancers.

Heat-shock protein-90 plays a role in the proper folding of the ERBB2 protein following its biosynthesis in the ribosome. By inhibiting this chaperone function of heat-shock protein-90 with inhibitors such as tanespimycin (also known as 17-AAG), the stability of ERBB2 is undermined.

Finally, small molecular tyrosine kinase inhibitors have been developed that block the nucleotide-binding site within the intracellular domain of ERBB proteins. To date, only two ERBB2-targeted therapies, trastuzumab and lapatinib (Tykerb®; GlaxoSmithKline, Research Triangle Park, NC), have been approved by the FDA for clinical use in ERBB2-positive breast cancer patients. The reversible small molecule tyrosine kinase inhibitor, lapatinib, inhibits both ERBB1 and ERBB2, but its clinical utility for breast cancer is largely limited to ERBB2-positive disease. Since 2007, it has been approved by the FDA for use in combination with capecitabine (Xeloda®; F. Hoffmann-La Roche, Basel, Switzerland) for the treatment of patients with advanced or metastatic breast cancers overexpressing the ERBB2 protein who have failed previous therapies, including anthracyclines, a taxane, and trastuzumab. This review will discuss certain advantages of lapatinib and its utility in the clinical setting, its pharmacology, pharmacokinetics, efficacy and tolerability,
and briefly introduce some of the investigational new clinical studies of lapatinib.

**Pharmacology of lapatinib**

Lapatinib (originally known as GW572016) is a small molecule kinase inhibitor and derivative of 4-anilinoquinoline. It targets both ERBB1 and ERBB2 by reversibly attaching to the intracellular adenosine triphosphate binding site of the kinases.\(^3\) This inhibits the phosphorylation and subsequent activation of the PI3K-Akt and Ras-Raf-mitogen-activated protein kinase signaling cascades, increasing apoptotic activity and decreasing cellular proliferation (see Figure 1).\(^3\)

Lapatinib has a large aniline quinazoline head group which allows access deep into the catalytic cleft of ERBB1.\(^3\) This is a possible explanation for lapatinib’s slow dissociation half-life of >300 minutes in comparison with other quinazolines, such as erlotinib (Tarceva®; OSI/Genentech, Long Island, NY) and consequently longer inhibition of ERBB1.\(^3\) The 50% inhibitory concentration is <0.2 µM for both ERBB1 and ERBB2, establishing lapatinib as a potent inhibitor.

Certain ERBB2-positive breast cancer lines express an amino terminally truncated carboxyl terminal fragment of ERBB2, p9\(^5\)ERBB2, which may arise either by proteolytic cleavage or by alternative translation of the ERBB2 mRNA transcript.\(^3\) These truncated ERBB2 isoforms retain potent tyrosine kinase activity,\(^4\) and lines are resistant to trastuzumab because p9\(^5\)ERBB2 lacks the extracellular binding domain to which trastuzumab binds. Although the biologic function and frequency of p9\(^5\)ERBB2 expression in clinical ERBB2-positive breast cancers has not yet been exhaustively evaluated, this catalytically active truncated p9\(^5\)ERBB2 has been demonstrated in a number of studies of primary ERBB2 human breast cancers and may constitute a major mechanism of trastuzumab resistance.\(^4\)

The expression of truncated ERBB2 isoforms is more common in metastatic than in primary ERBB2-positive breast cancers and is a predictor of worse outcome in metastatic breast cancer patients.\(^4\) Moreover, serum levels of

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**Figure 1** Mechanism of action of lapatinib. ERBB2 homodimerization or heterodimerization with other family members is promoted by binding of ligand (such as epidermal growth factor), and possibly by high receptor density secondary to ERBB2 amplification. Two key signaling pathways activated by receptor dimerization and activation are the PI3K-Akt pathway, which promotes both cell survival and cell cycle progression, and the mitogen-activated protein kinase (MAPK) pathway, which stimulates proliferation. Lapatinib blocks the catalytic cleft of the ERBB1 and ERBB2 receptors, thereby preventing adenosine triphosphate binding and subsequent receptor phosphorylation leading to inhibition of downstream mitogenic signaling cascades.
ERBB2 extracellular domain were associated with resistance to trastuzumab in a large multicenter study\(^4^4\) and the presence of truncated ERBB2 whether in serum or the tumor is also correlated with a decreased response to trastuzumab and poor outcome in patients with ERBB2-positive breast cancer.\(^4^0,4^3,4^8\)

In contrast with trastuzumab which cannot bind and inhibit p95\(^{ERBB2}\), lapatinib binds to the catalytic cleft and can inhibit p95\(^{ERBB2}\), and thus lapatinib can overcome p95\(^{ERBB2}\)-mediated trastuzumab resistance. Lapatinib has been shown to inhibit downstream mitogenic signaling cascades in cell lines expressing p95\(^{ERBB2}\) and to block their growth in vitro and in vivo.\(^4^0\) Scaltriti et al demonstrated that treatment of p95\(^{ERBB2}\)-expressing breast cancer lines with lapatinib inhibited p95\(^{ERBB2}\) phosphorylation and reduced Akt and mitogen-activated protein kinase phosphorylation. These p95\(^{ERBB2}\)-expressing cell lines were trastuzumab-resistant but retained sensitivity to the antiproliferative effects of lapatinib.\(^4^0\) This study provides support for further characterization of ERBB2-positive breast tumors based on the presence or absence of p95\(^{ERBB2}\) to help determine an optimal anti-ERBB2 therapy. Several other preclinical studies have also shown that lapatinib retains efficacy in trastuzumab-resistant cancer models.\(^3^7,4^9,5^0\)

### Pharmacokinetics of lapatinib

Bence et al evaluated the safety, tolerability, and pharmacokinetics of lapatinib as a single- and multiple-dose agent in a double-blind, randomized, placebo-controlled Phase I study.\(^4^1\) The results indicated that lapatinib was well tolerated in both regimens and not associated with any serious adverse events. In patients who received single doses, the most common adverse events were headache (23%), rash (9%), cough/cold (6%), diarrhea (4%), and chalky taste (4%). Of the 23 adverse events recorded in the 47 subject lapatinib dosing periods, only one subject had an adverse event greater than Grade 1. The multiple-dose study of lapatinib also reported that the drug was well tolerated with no serious adverse events. Gastrointestinal discomfort was the most common adverse event in 27% of the subjects who received lapatinib. Other adverse events included elevated liver function tests (17%), rash (11%), and headache (6%). Of the 28 adverse events observed in subjects receiving either lapatinib or placebo, five were Grade 2 and resolved without treatment.

In this single-dose study, peak drug concentrations were reached approximately 3–4 hours after administration. The mean half-life was in the range 6–9 hours and increased as doses were raised. The multiple-dose study showed peak drug concentrations within 3–4 hours with no significant or consistent change over time. The average half-life was approximately seven hours on day 1 for all doses and 11 hours at 175 mg on day 8. Steady-state concentrations were achieved in six and seven days at the 100 mg and 175 mg doses, respectively.

The pharmacokinetics of lapatinib are summarized in the Table 1. At the 1250 mg/day dose approved by the FDA, the time to peak concentration (\(T_{\text{max}}\)), peak concentration (\(C_{\text{max}}\)), and area under the concentration-time curve (AUC) are 3–4 hours, 2.43 \(\mu\)g/mL, and 36.2 \(\mu\)g⋅h/mL, respectively.\(^3^3,5^2–5^4\) The effective half-life of daily dosing of lapatinib is 24 hours. The steady-state AUC is increased by approximately twofold if lapatinib is administered in divided daily doses compared with drug administration once daily at the same total dose.\(^3^3,5^3\) Lapatinib is highly bound (>99%) to albumin and \(\alpha\)-1 acid glycoprotein at 1 \(\mu\)mol/L.\(^3^3,5^3\) In vitro studies revealed that lapatinib is a substrate for and an inhibitor of P-glycoprotein.\(^3^3,5^3\) Further, it has a broad distribution with a volume of distribution of >2200 L that is significantly greater than the volume of body water.\(^1^0,5^2,5^3\)

Elimination of lapatinib occurs through fecal excretion and hepatic metabolism via cytochrome P450 (CYP3A4, CYP3A5, CYP2C19, and CYP2C8), with 70% through CYP3A4.\(^3^3,5^3–5^5\) Almost one-third (27%) of an oral dose is recovered in feces and <2% is recovered in urine with an elimination half-life of 14.2 hours in single-dose studies and approximately 24 hours with repeated dosing due to drug accumulation.\(^3^3,5^3\)

Lapatinib is both a substrate and inhibitor of CYP3A4 and an inhibitor of CYP2C8 in vitro. A clinical study in healthy volunteers showed that when ketoconazole, a CYP3A4 inhib-

### Table 1 Review of the pharmacokinetics of lapatinib at the dose of 1250 mg/day, approved by the Food and Drug Administration

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Oral, not available in IV form</td>
</tr>
<tr>
<td>(T_{\text{max}})</td>
<td>3–4 hours</td>
</tr>
<tr>
<td>Steady-state (C_{\text{max}})</td>
<td>2.43 (\mu)g/mL</td>
</tr>
<tr>
<td>AUC</td>
<td>36.2 (\mu)g⋅h/mL</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>Highly bound (&gt;99%) to albumin</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP3A4 (70% of metabolism)</td>
</tr>
<tr>
<td></td>
<td>CYP3A5, CYP2C19, CYP2C8</td>
</tr>
<tr>
<td>Elimination</td>
<td>Primarily hepatic</td>
</tr>
<tr>
<td>Single dose (t_{\frac{1}{2}})</td>
<td>14.2 hours</td>
</tr>
<tr>
<td>Multiple doses (t_{\frac{1}{2}})</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

**Abbreviations:** \(t_{\frac{1}{2}}\) elimination half-life; AUC, area under the concentration-time curve; IV, intravenous; \(T_{\text{max}}\), time to peak concentration; \(C_{\text{max}}\), maximum concentration.
itor, was administered, there was a 3.6-fold increase in the AUC of lapatinib and a 1.7-fold increase in elimination half-life relative to the control.33,53 By contrast, carbamazepine (Tegretol®; Novartis International AG, Basel, Switzerland), a CYP3A4 inducer, reduced the AUC of lapatinib by 72%.33 Thus, strong CYP2C8 and CYP3A4 inhibitors (eg, grapefruit, clarithromycin, azole antifungals, and antiretrovirals) should be avoided to reduce risks of increased lapatinib plasma concentrations and, subsequently, lapatinib toxicity.

Clinical trials
Monotherapy
In 2008 Burstein et al reported the results of a multinational, open-label Phase II trial that evaluated the tolerability and efficacy of lapatinib monotherapy in patients with advanced or refractory metastatic breast cancer who had progressed on anthracycline, taxane, capecitabine, and trastuzumab therapies.56 The study comprised two cohorts: cohort A consisted of 140 patients with ERBB2-positive tumors; cohort B consisted of 89 patients with ERBB2-negative tumors. Patients from each cohort received lapatinib 1500 mg daily at a minimum of one hour before or after breakfast. Using the Response Evaluation Criteria in Solid Tumors, ERBB2-negative tumors from cohort B did not exhibit objective responses. In cohort A, where patients’ tumors were ERBB2-positive, there were three partial responses and three complete responses, leading to a response rate (complete response + partial response) of 4.3% by investigators’ assessment or 1.4% (two partial responses) by independent review.56 A clinical benefit rate (complete response, partial response + stable disease ≥ 24 weeks) was observed in 5.7% of the ERBB2-positive patients.

Independent review assessment of median time to tumor progression and median progression-free survival were similar for both ERBB2-positive and ERBB2-negative cohorts (9.1 weeks and 7.6 weeks, respectively). Median survival was 29.4 weeks in ERBB2-positive patients and 18.6 weeks in ERBB2-negative patients.

Two open-label Phase II trials that evaluated the safety and efficacy of lapatinib monotherapy in patients with trastuzumab-refractory, ERBB2-positive advanced or metastatic breast cancer found similar results. Blackwell et al evaluated 78 patients with ERBB2-positive metastatic breast cancer refractory to trastuzumab and found a clinical benefit rate (complete response, partial response + stable disease ≥ 16 weeks) of 21.8% and a partial response rate of 7.7%.57 Patients were treated with either 1250 mg or 1500 mg daily after protocol amendment. The study concluded that lapatinib as a single agent has clinical activity associated with manageable toxic effects, the most common being rash (47%), diarrhea (46%), and nausea (31%). Another open-label Phase II trial conducted in Japan of 45 patients with ERBB2-positive metastatic breast cancer refractory to previous anthracycline, taxane, capecitabine, and trastuzumab therapy showed a clinical benefit rate (complete response, partial response, + stable disease ≥ 24 weeks) of 33.3%.58

Gomez et al reported the results of a randomized, open-label Phase II study of lapatinib as first-line monotherapy for ERBB2-positive advanced or metastatic breast cancer.59 Patients were randomly assigned to one of two dose groups and received either 1500 mg once daily or 500 mg twice daily. Seventy-six percent of the patients had both estrogen receptor- and progesterone receptor-negative tumors. Overall, there was a 24% response rate, clinical benefit rate (complete response, partial response, + stable disease ≥24 weeks) of 31%, progression-free survival at six months, and no significant difference in outcomes between the two groups.

Lapatinib-chemotherapy combinations
A 2006 study that compared lapatinib plus capecitabine with capecitabine alone established that the combination therapeutic regimen is superior to capecitabine monotherapy in women with ERBB2-positive advanced breast cancer whose disease has progressed after anthracycline, taxane, or trastuzumab treatments.34 The primary endpoint was time to tumor progression (hazard ratio [HR] = 0.49; 95% confidence interval [CI]: 0.34–0.71; P < 0.001). Three hundred twenty-four women were randomly assigned to receive oral lapatinib 1250 mg daily plus capecitabine 2000 mg/m² given in two divided doses on days 1–14 of a 21-day cycle, or capecitabine monotherapy at 2500 mg/m² given in two divided doses on days 1–14 of a 21-day cycle. The results showed an increased median time to tumor progression for patients in the combination arm compared with those on the monotherapy regimen (8.4 months versus 4.4 months, respectively). Moreover, these results were achieved without compromising cardiac function or increasing toxicity.

Another multicenter, randomized, double-blind, placebo-controlled Phase III study comparing lapatinib plus paclitaxel versus paclitaxel alone for first-line treatment in 580 women with metastatic disease was reported in 2007.46 Patients were randomized into two groups where one received oral lapatinib 1500 mg daily plus paclitaxel 175 mg/m² every three weeks and the other group received placebo plus paclitaxel 175 mg/m² every three weeks. In an intent-to-treat analysis of investigators’ assessments, the ERBB2 untested
or unknown population that received combination therapy had a significantly higher response rate when compared with paclitaxel monotherapy (35.1% versus 25.3%, respectively; \(P = 0.008\)). The clinical benefit rate at six months was also significantly higher with combination therapy than with paclitaxel monotherapy (40.5% versus 31.9%; \(P = 0.025\)). However, no significant differences in the median duration of response, time to tumor progression, or overall survival were observed. When the results were evaluated by ERBB2-status subset analysis, patients with ERBB2 amplification who received combination therapy had significant improvement in response rate compared with the paclitaxel monotherapy regimen (60% versus 36%; \(P = 0.027\)) and improved median time to tumor progression (6.1 versus 5.8 months; \(P = 0.011\)). In the ERBB2-untested population, combination therapy showed no improvement over monotherapy (time to tumor progression 6.7 versus 5.3 months, respectively).

**Lapatinib-hormonal therapy combinations**

Resistance to endocrine therapy poses a challenge in the treatment of hormone receptor-positive metastatic breast cancers. Cross-talk between pathways involving ERBB receptors and hormone receptors appears to contribute to endocrine therapy resistance.\(^{61-65}\) ERBB2-overexpression confers resistance to established endocrine therapies, and patients with hormone receptor-positive and ERBB2-positive metastatic breast cancers who were treated with trastuzumab combined with the aromatase inhibitor, anastrozole (Arimidex\(^{\text{®}}\); AstraZeneca, London, UK), had twice the median progression-free survival when compared with those treated with anastrozole alone (2.4 versus 4.8 months, respectively).\(^{62,66-69}\) Consequently, to overcome endocrine resistance, therapies combining ERBB2 pathway inhibitors with endocrine manipulation have been studied.

Preclinical studies evaluated the potential of lapatinib in combination with estrogen receptor blockade by tamoxifen (Nolvadex\(^{\text{®}}\); AstraZeneca) to restore responsiveness to tamoxifen-resistant breast cancers in culture and in xenograft tumors in mice. Chu et al reported that combined treatment with tamoxifen and lapatinib caused a greater increase in the cell cycle inhibitor, p27, and in p27-mediated cell cycle arrest in G\(_1\) phase than was observed with either drug alone.\(^2\) In breast cancer xenograft studies, tumors that were originally tamoxifen-stimulated showed inhibition by combined lapatinib plus tamoxifen.

In 2009, a Phase III study was reported that evaluated addition of lapatinib to the aromatase inhibitor, letrozole (Femara\(^{\text{®}}\); Novartis International AG), as a first-line treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women (\(n = 1286\)).\(^{70}\) Patients were randomized to receive daily treatment with 2.5 mg of letrozole plus 1500 mg of lapatinib or 2.5 mg letrozole plus placebo. While addition of lapatinib to letrozole therapy did not provide additional benefit in this postmenopausal patient group overall, the subset analysis of ERBB2-positive cancers was instructive. Two hundred nineteen of the 1286 patients enrolled had ERBB2-overexpressing tumors. Using progression-free survival as the primary endpoint in the ERBB2-overexpressing cancers, the analysis revealed that the addition of lapatinib to letrozole significantly lowered risk of disease progression compared with letrozole alone (HR = 0.71; 95% CI: 0.53–0.96; \(P = 0.019\)) where the progression-free survival was 8.2 months versus 3.0 months, respectively. The objective response rate (28% versus 15%; odds ratio [OR], 0.4; 95% CI: 0.2–0.9; \(P = 0.21\)) and clinical benefit rate (48% versus 29%; OR, 0.4; 95% CI: 0.2–0.8; \(P = 0.003\)) were also significantly greater in the lapatinib plus letrozole-treated ERBB2-overexpressing cancers. On the other hand, patients whose cancers were ERBB2-negative (\(n = 952\)) did not show improvement in progression-free survival. As of February 2010, lapatinib plus letrozole is now an FDA-approved regimen for hormone receptor-positive and ERBB2-overexpressing postmenopausal metastatic breast cancers.\(^{71}\)

**Lapatinib-trastuzumab combinations**

Konecny et al investigated the therapeutic potential of lapatinib by examining its effect on the growth of 31 trastuzumab-resistant ERBB-2 positive human breast cancer cell lines.\(^{50}\) Concentration-dependent antiproliferative effects of lapatinib were seen in all cell lines tested. However, the extent of growth inhibition by lapatinib varied widely between individual cell lines and was significantly correlated with level of ERBB2 expression. ERBB2 gene amplification and ERBB2 protein overexpression were associated with a higher sensitivity to lapatinib in vitro across the tested cell lines. Significant reduction in the volume of human breast cancer xenografts in athymic mice was observed with lapatinib when compared with untreated controls. Synergistic drug interactions between lapatinib and trastuzumab were also seen in four different ERBB2-overexpressing cell lines. This study, reported in 2006, provided the biologic rationale to test lapatinib as a single agent or in combination with trastuzumab in ERBB2-overexpressing patients with clinical resistance to trastuzumab.

Clinical trials of lapatinib in conjunction with trastuzumab have tested the potential superiority of this combination...
over lapatinib monotherapy for trastuzumab-resistant metastatic breast cancer. The activity of lapatinib in combination with trastuzumab in patients with advanced, ERBB2-positive, trastuzumab-refractory metastatic breast cancer was reported in 2008. This Phase I study evaluated this regimen’s safety, optimally tolerated regimen, and pharmacokinetics. 

Cohorts of three patients were treated with escalating doses of lapatinib from 750 mg to 1500 mg administered once daily in combination with trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly). Additional patients were enrolled to evaluate the pharmacokinetics of both agents alone and in combination, once the optimally tolerated regimen was determined. The dose-limiting toxicities of a sequence of dose levels were studied. Based on the two dose-limiting toxicities reported at 1250 mg lapatinib with trastuzumab, and the higher frequency of fatigue impacting tolerability, the combination dose of lapatinib 1000 mg and with standard weekly trastuzumab was selected as the optimally tolerated regimen.

A subsequent Phase II study evaluated the coadministration of trastuzumab and lapatinib versus lapatinib alone in metastatic ERBB2-positive disease refractory to trastuzumab therapy and showed that patients receiving combined treatment had a significantly improved median progression-free survival (12 months versus 8.1 months), a 27% reduction in risk of disease progression \( (P = 0.008), \) an increased clinical benefit rate \( (24.7\% \text{ versus } 12.4\%), \) a greater tumor response rate \( (10.3\% \text{ versus } 6.9\%) \) and a trend toward improved survival. 

An updated survival analysis, reported by Blackwell et al in 2009, concluded that combination therapy with lapatinib plus trastuzumab was superior to lapatinib alone. The median overall survival of 60.7 weeks for combination therapy was significantly higher than the overall survival of 41.4 weeks for lapatinib alone \( (HR 0.74; 95\% \text{ CI: } 0.57–0.97; \ P = 0.026). \) Further, the survival benefit was maintained upon adjusting for baseline prognostic factors \( (HR 0.71; 95\% \text{ CI: } 0.54–0.93; \ P = 0.012). \) Further clinical trials evaluating trastuzumab-lapatinib combination therapy are currently underway in metastatic and early breast cancer.

**Lapatinib and inflammatory breast cancer**

Although the incidence of inflammatory breast cancer is low (<5% of breast cancers) in the US, this form of breast cancer is very aggressive, affects a younger population, and has a low overall survival. Inflammatory breast cancer is characterized by rapid onset of swelling and erythema of the breast, and often does not present with a palpable breast mass. Dermal lymphatic invasion is characteristic of this disease which often shows overexpression of ERBB2. Lapatinib has exhibited encouraging activity in inflammatory breast cancer. A Phase I trial showed four clinical responses (complete response/partial response) in five patients with inflammatory breast cancer treated with lapatinib and led to Phase II studies that are continuing the evaluation of lapatinib in inflammatory breast cancer.

Johnston et al conducted a Phase II study in patients with recurrent or anthracycline refractory inflammatory breast cancer who had not received previous trastuzumab therapy. The 45 enrolled patients were grouped into two cohorts based on their ERBB2 and ERBB1 profiles (cohort A: ERBB2-positive; cohort B: ERBB2-negative and ERBB1-positive). Fifty percent of cohort A (15 of 30 patients) exhibited a clinical response, while only 6.7% (one of 15 patients) in cohort B had a clinical response. Tumor markers predictive of lapatinib response in cohort A included phosphorylated ERBB3 expression \( (P = 0.021), \) phosphorylated ERBB2/ERBB3 coexpression \( (P = 0.005), \) and absence of p53 expression \( (P = 0.033). \)

Another Phase II trial reported by Spector et al, which evaluated lapatinib monotherapy for treatment-refractory inflammatory breast cancer, indicated that high ERBB2, phosphorylated-ERBB2, and IGF-IR coexpression are predictors for clinical response to lapatinib monotherapy in patients with treatment-resistant inflammatory breast cancer. ERBB2 overexpression, but not ERBB1 expression alone, indicates sensitivity to lapatinib in inflammatory breast cancer. Seventeen patients were evaluated from the 34 patients enrolled. Cohort A was comprised of ERBB2-positive patients, irrespective of ERBB1 status, while cohort B consisted of patients with ERBB1-positive and ERBB2-negative tumors. Cohort A showed clinical responses in eight of the 11 patients, whereas none of the six patients in cohort B showed any clinical response.

Expanding on these findings, Kaufman et al reported on an open-label Phase II study of 1500 mg of lapatinib given once daily in 126 patients with relapsed or refractory ERBB2-positive inflammatory breast cancer. Although none of the patients had a complete response, 39% of the patients had an overall response. The findings included a median response of 19.4 months \( (95\% \text{ CI: } 12.8–26.4) \) and a median overall survival of 11.2 months \( (95\% \text{ CI: } 9.1–13.5) \) for patients who responded to lapatinib, compared with a median overall survival of 8.4 months \( (95\% \text{ CI: } 5.9–9.4) \) for nonresponders to lapatinib.

An open-label Phase II study in 23 patients with newly diagnosed inflammatory breast cancer treated with lapatinib...
in combination with paclitaxel as neoadjuvant therapy showed a clinical response in 95% (20/21) patients with ERBB2-positive tumors and in two of two patients with ERBB1-positive/ERBB2-negative tumors. These encouraging results support further clinical investigation of combination regimens containing lapatinib prior to surgery for inflammatory breast cancer patients.

Treatment of central nervous system metastasis

It has been estimated that 15% of advanced breast cancer patients develop symptomatic brain metastases. A meta-analysis of the randomized controlled trials evaluating trastuzumab treatment in early breast cancer found that development of brain metastasis was significantly higher for trastuzumab-treated patients \( (P = 0.033) \), but is overall low-risk (0.62%). Unfortunately, other than treatment with steroids, radiotherapy or surgery, no treatment currently provides long-term efficacy for brain metastases. It has been postulated that due to its small size, lapatinib may circumvent this problem by permeating the central nervous system to prevent or reduce brain metastases.

In a 2008 open-label Phase II trial, Lin et al reported early evidence for a clinical benefit when ERBB2-positive breast cancer patients with new or progressive brain metastases were given lapatinib monotherapy at a starting dose of 750 mg twice a day in four-week cycles. Thirty-nine patients who had developed brain metastases while receiving trastuzumab were evaluated. Eligibility requirements included prior trastuzumab and documented central nervous system progression after radiation therapy. If patients had not received previous radiation therapy, the patients were required to be asymptomatic. The median time to tumor progression was three months (95% CI: 2.3–3.7) and 11.3 months for the one patient with a central nervous system objective response. Seven patients were progression-free in both central nervous system and noncentral nervous system sites at 16 weeks, and three patients had a decline in volume of central nervous system metastasis of >30%.

Since both capecitabine and lapatinib have potential efficacy for central nervous system disease, these initial data with lapatinib monotherapy prompted Geyer et al to suggest that combination lapatinib and capecitabine therapy may delay progression or even prevent the onset of central nervous system metastasis. Data from trials comparing trastuzumab and lapatinib in the adjuvant and neoadjuvant settings should yield information on their respective abilities to reduce subsequent brain metastasis and are eagerly awaited.

Adminstration

The following presents administration guidelines for FDA-approved uses of lapatinib. Lapatinib is administered in 250 mg tablets in combination with capecitabine over 21-day cycles. The recommended dosage of lapatinib for patients with advanced or metastatic breast cancer who are positive for ERBB2 and have previously received therapy including an anthracycline, a taxane, and trastuzumab, is 1250 mg given once daily on days 1–21 continuously in combination with capecitabine at 2000 mg/m²/day (administered orally two times a day) on days 1–14. While whole tablets of lapatinib should be administered on an empty stomach, one hour before or after a meal, capecitabine should be taken on a full stomach. As stated previously, since lapatinib is an inhibitor of CYP3A4, if coadministration of a CYP3A4 inhibitor is necessary, a dose reduction of lapatinib to 500 mg/day may be considered. Additionally, due to gastric pH fluctuations, antacids should be avoided for one hour before and after lapatinib administration.

As of 2010, lapatinib is indicated for use in combination with letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer with ERBB2 overexpression. In combination with letrozole, the recommended dosage of lapatinib is 1500 mg given once daily continuously in combination with letrozole. When coadministered with lapatinib, the recommended dose of letrozole is 2.5 mg once daily.

Patients should be monitored for cardiac, pulmonary, and hepatic function while on a lapatinib regimen. Left ventricular ejection fraction should be evaluated in all patients prior to the initiation of treatment with lapatinib as a baseline, using means such as echocardiography or multiple-gated acquisition scans. Pulmonary symptoms indicative of interstitial lung disease or pneumonitis should also be monitored in all patients. Patients’ liver function tests, including transaminases, bilirubin, and alkaline phosphatase, should also be examined prior to treatment and every 4–6 weeks during treatment. Further, because myelosuppression is an adverse effect of capecitabine, complete blood counts should be performed according to the treating physician’s judgment.

Adverse effects and tolerability

Studies have shown lapatinib to be a generally well tolerated drug. The most common clinical toxicities related to lapatinib monotherapy administered at 1500 mg once daily in the Phase II study conducted by Burstein et al were diarrhea (54%), rash (30%), nausea (24%), vomiting (14%), fatigue
(14%), and anorexia (10%). These adverse effects were mostly Grade 1 or 2 in severity, with a maximum severity of Grade 3 by National Cancer Institute Common Terminology Criteria for Adverse Events.

When used in combination regimens, lapatinib-related adverse effects are increased. Geyer et al reported the most common adverse events from lapatinib plus capecitabine therapy were diarrhea (60%), palmar-plantar erythrodysesthesia (hand-foot) syndrome (49%), nausea (44%), rash (27%), vomiting (26%), and fatigue (18%), with most events of Grade 1, 2, or 3 severity. Two of 163 (1%) women who received combination therapy with capecitabine experienced Grade 4 diarrhea. When lapatinib was combined with letrozole, the most common adverse reactions were diarrhea (64%), rash (44%), nausea (31%), fatigue (20%), and arthralgia (19%), with the majority being Grade 1 or 2. Sixty patients (10%) who received lapatinib plus letrozole combination therapy had Grade 3 or 4 diarrhea.

Lapatinib-associated cardiac toxicity has been reported at a low frequency. Cardiac toxicity was an unexpected adverse event found from early preclinical trials of trastuzumab metastatic breast cancer patients. Because cardiac toxicity was a serious toxicity in the pivotal Phase III trial of trastuzumab in the treatment of metastatic breast cancer, there was initial concern about the potential cardiotoxicity of lapatinib. However, Burstein et al reported only one patient who had a Grade 3 decrease in left ventricular ejection fraction. Lin et al reported no cases of symptomatic congestive heart failure, although four patients who had received a median of two previous trastuzumab-containing chemotherapy regimens had asymptomatic decreases in left ventricular ejection fraction to <50%. A pooled analysis of trials involving over 12,000 patients revealed that cardiac toxicity was observed in only 0.4–4% of patients. A retrospective analysis of lapatinib-associated cardiac toxicity was conducted by Perez et al in 3689 lapatinib-treated patients. Data from 44 Phase I–III clinical studies of lapatinib monotherapy and combination therapy showed low levels of cardiotoxicity for lapatinib. Cardiac events were reported in 60 patients (1.6%). These patients had previously been treated with anthracyclines (n = 12), trastuzumab (n = 14), or neither (n = 34). Overall, no cardiac mortality was recorded. The study concluded that cardiac events were usually asymptomatic, caused reversible decreases in left ventricular ejection fraction, and occurred at similar rates in patients who had and had not received previous treatments with anthracyclines and trastuzumab. Although the long-term cardiac effects of lapatinib are not known at present, re-evaluation of long-term follow-up data will ultimately be forthcoming.

Cost considerations
The wholesale price of lapatinib in the US is on average $26 per 250 mg tablet. At the recommended 1250 mg/day dosage, the therapy currently costs approximately $130 per day or $2800 for each 21-day cycle. To assess the total cost of lapatinib treatment, combination agents such as capecitabine and letrozole need to be included. The cost-benefit analysis for this agent is a serious consideration for developing nations and for countries with limited resources for health care delivery.

Conclusion
A myriad of targeted therapies have emerged that show activity against ERBB2-positive breast cancers. The use of lapatinib as monotherapy or in combination with conventional cancer treatments is currently being assessed in various clinical trials. Although lapatinib is a small molecule tyrosine kinase inhibitor of both ERBB1 and ERBB2, its action appears to be limited to ERBB2-positive disease. It has been approved for use in combination with capecitabine in the treatment of ERBB2-positive metastatic breast cancer patients whose disease has progressed after trastuzumab therapy and in combination with letrozole for the treatment of postmenopausal women with ERBB2-positive and hormone receptor-positive metastatic breast cancer. Lapatinib monotherapy is generally well tolerated and is not associated with cardiotoxicity.

Further trials evaluating lapatinib are currently ongoing. Two large world-wide randomized studies, ALTTO and Neo-ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization), will investigate lapatinib alone or in combination with trastuzumab in the adjuvant and neoadjuvant settings, respectively, in patients with early ERBB2-positive breast cancer. These international, randomized, open-label Phase III trials intend to enroll 8000 patients with ERBB2-positive breast cancers. Other trials, including the investigation of lapatinib with other chemotherapeutic agents, such as vinorelbine (Navelbine®; GlaxoSmithKline), and lapatinib in combination with letrozole in the neoadjuvant setting, are also in development.

Disclosure
The authors report no conflicts of interest in this work.
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