Lapatinib for Advanced or Metastatic Breast Cancer

FRANS L. OPDAM,^{a,b} HENK-JAN GUCHELAAR,^b JOS H. BEIJNEN,^{c,d} JAN H.M. SCHELLENS^{a,d}

^aDepartment of Clinical Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands;

^bDepartment of Clinical Pharmacy and Toxicology, Leiden University Medical Hospital, Leiden, The Netherlands; ^cDepartment of Pharmacy and Toxicology, Slotervaart Hospital, Amsterdam, The Netherlands;

^dUtrecht University, Faculty of Science, Department of Pharmaceutical Sciences, Section of Biomedical Analysis, Division of Drug Toxicology & Pharmaco-epidemiology and Clinical Pharmacology, Utrecht, The Netherlands

Key Words. Lapatinib • Clinical pharmacology • EGFR • HER-2 • Breast cancer • Review

Disclosures: Jan H.M. Schellens: Roche, GlaxoSmithKline, Eisai (RF). The other author(s) indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

ABSTRACT

Lapatinib is a potent reversible and selective inhibitor of the tyrosine kinase domains of epidermal growth factor receptor and human epidermal growth factor receptor (HER)-2 that exerts its action by competitive binding to the intracellular ATP-binding site of the receptor. It is registered for the treatment of advanced or metastatic HER-2⁺ breast cancer in combination with capecitabine and for hormone receptor–positive breast cancer in combination with an aromatase inhibitor. Lapatinib administered

orally once daily is moderately to well tolerated, with rash and gastrointestinal adverse events as the main toxicities. In studies on the efficacy of lapatinib, direct comparisons between lapatinib and trastuzumab are lacking. Results of ongoing randomized phase III studies with lapatinib or trastuzumab in combination with taxanes as first-line agents for metastatic breast cancer as well as in the neoadjuvant and adjuvant settings are awaited. *The Oncologist* 2012;17:536–542

INTRODUCTION

Lapatinib (in Europe: Tyverb®; GlaxoSmithKline, Uxbridge, U.K.; in the U.S.: Tykerb®; GlaxoSmithKline, Philadelphia) is currently registered for two indications: (a) in Europe and in the U.S. in combination with capecitabine for patients with advanced breast cancer or metastatic breast cancer (MBC) whose tumors overexpress human epidermal growth factor receptor (HER)-2 (ErbB-2) and are progressive after prior therapy, which must have included anthracyclines and taxanes, and therapy with trastuzumab in the advanced disease setting [1, 2]; (b) in Europe in combination with an aromatase inhibitor for postmenopausal women with hormone receptor (HR)⁺ and HER-2⁺ MBC not currently intended for chemotherapy [1] and in the U.S. in combination with letro-

zole for the treatment of postmenopausal women with HR⁺ MBC that overexpress the HER-2 and for whom hormonal therapy is indicated [3].

HER-2 protein overexpression is present in 20%–25% of human breast cancers. Patients with HER-2⁺ breast cancer have been reported to have shorter disease-free survival and overall survival (OS) times than patients with HER-2[−] tumors [4], and therefore this is a negative prognostic characteristic. Trastuzumab was the first registered anti-HER-2 agent that, when combined with chemotherapy, resulted in a longer time to progression (TTP), greater response rate (RR), and longer OS time in patients with HER-2⁺ MBC [5]. Lapatinib is an oral drug, combining inhibition of HER-2 and epidermal growth factor receptor (EGFR, HER-1) tyrosine kinases.

Correspondence: Jan H.M. Schellens, M.D., Ph.D., The Netherlands Cancer Institute, Department of Clinical Pharmacology, Postbus 90203, 1006 BE Amsterdam, The Netherlands. Telephone: 0031-205122446; Fax: 0031-205122572; e-mail: j.schellens@nki.nl Received December 23, 2011; accepted for publication February 28, 2012; first published online in *The Oncologist Express* on April 3, 2012. ©AlphaMed Press 1083-7159/2012/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2011-0461>

CLINICAL USE

Lapatinib is available in tablets of 250 mg. The recommended dose of lapatinib in combination with capecitabine is 1,250 mg once daily continuously. In combination with an aromatase inhibitor, the recommended dose is 1,500 mg once daily continuously.

All tablets should be taken together at the same time, at least 1 hour before or 1 hour after a meal [1].

MECHANISM OF ACTION

Lapatinib (Fig. 1A) is a potent reversible and selective inhibitor of the intracellular domains of the tyrosine kinases EGFR (HER-1) and HER-2. It competes with ATP for the ATP-binding pocket. This leads to downstream blocking of the mitogen-activated protein kinase and phosphatidylinositol 3-kinase, Akt, and mammalian target of rapamycin dependent transduction pathways, resulting in growth arrest or apoptosis of tumor cells [6, 7] (Fig. 1B).

Unlike trastuzumab, lapatinib is able to bind and inhibit p95^{HER-2}, which is the truncated form of HER-2 lacking an extracellular domain but possessing greater kinase activity than wild-type HER-2. Trastuzumab resistance may be mediated, at least in part, through the expression of p95^{HER-2} in disease progression [8].

ANALYTICAL METHODOLOGY

The bioanalysis of lapatinib can be exerted by high-performance liquid chromatography with tandem mass spectrometry detection [9].

PHARMACOKINETICS

Absorption

After oral administration, the maximum plasma concentration of lapatinib is achieved within 3–4 hours [10]. The bioavailability of lapatinib is highly influenced by concomitant food intake, with the largest effect being seen with a high-fat meal, which increases the exposure of lapatinib more than threefold. Because greater bioavailability in the fed state does not significantly decrease the large interpatient variability, it is recommended to administer the drug in the fasted state to obtain consistent therapeutic exposure [11].

The solubility of lapatinib is pH dependent. Proton pump inhibitors and other agents that increase gastric pH should be avoided because they may negatively affect the absorption of lapatinib [1].

Distribution

Lapatinib is ~99% bound to albumin and α 1-acid glycoprotein (Table 1). In spite of high plasma protein binding, the volume of distribution of the terminal phase is >2,200 l, much greater than the volume of body water, indicating high tissue distribution [12, 13]. The penetration of lapatinib into the central nervous system (CNS) is poor. In a mouse study, an important role of the drug transporters P-glycoprotein (P-gp, *mdr1*, *abcb1*) and BCRP-1 (human homolog BCRP, *ABCG2*) in limiting the uptake of lapatinib in the CNS was demonstrated, because in *abcb1/abcg2*

knockout mice, compared with normal mice, the normally very low CNS penetration was found to be 40-fold higher [14].

Metabolism

After oral uptake, lapatinib is metabolized to oxidation products by cytochrome P450 (CYP)3A4, 3A5, 2C19, and 2C8. The most important is CYP3A4, which accounts for ~70% of metabolism. One metabolite (GW690006), which accounts for <15% of metabolism, remains active against EGFR; however, it has lost activity against HER-2, whereas other metabolites appear to be inactive [12].

Elimination

Lapatinib is primarily eliminated by the liver, with <2% eliminated by the kidneys. The elimination half-life is ~14 hours after administration of a single dose, and ~24 hours after multiple dosing [12]. In a phase I study in patients with solid malignancies, lapatinib serum concentrations increased nearly in proportion with dose, indicating linear pharmacokinetics [15].

Drug and Complementary and Alternative Medicine Interactions

Lapatinib is an inhibitor of CYP3A4, most likely via modification of the enzyme by covalent binding of one of its metabolites [16]. In one study, lapatinib increased the area under the concentration–time curve (AUC) of SN-38, the active metabolite of the prodrug irinotecan, by 41%, the effect of which could be corrected for by dose adjustment of irinotecan. No other pharmacokinetic interactions were observed when combining lapatinib with 5-fluorouracil, leucovorin, and irinotecan [17].

In healthy volunteers, concomitant administration of the strong CYP3A4 inhibitor ketoconazole increased the AUC and prolonged the terminal half-life of lapatinib 3.6× and 1.7×, respectively [18]. Coadministration of lapatinib with strong inhibitors of CYP3A4 (e.g., ritonavir, saquinavir, ketoconazole, itraconazole, voriconazole, posaconazole, and nefazodone) should be avoided [1].

Alterations with Disease or Age

The influence of renal dysfunction on lapatinib clearance has not been studied yet; however, on theoretical grounds, considering the minimal renal elimination, no need for dose adjustments is expected [1, 12]. In a small group of patients with moderate or severe liver dysfunction (Child-Pugh score, 7–9 and >9, respectively), lapatinib exposure was 56% and 85% greater, respectively [1]. Therefore, a corresponding ≥50% dose reduction of lapatinib in patients with moderate to severe liver impairment should be considered. The safety of lapatinib in pregnancy and during breast feeding has not been established yet. There is a published case report of a woman who delivered a healthy baby despite exposure to lapatinib during 11 weeks in the first trimester [19]. However, lapatinib displayed reproductive toxicity in animals as well as growth retardation in pups exposed to lapatinib via breast feeding. Therefore, during pregnancy and lactation the use of lapatinib should be avoided [1].

Figure 1. Chemical structure of lapatinib and its inhibiting action in HER-1 and HER-2 signalling. **(A):** Chemical structure of lapatinib [44]. **(B):** Overview of the HER-2 signaling network. HER-2 exists as a homodimer and a heterodimer. Signaling through EGFR family dimers leads to the activation of downstream cascades, including the PI3K-, Akt-, and mTOR-dependent cell growth and differentiation pathways. The effects of this signaling can include dysregulation of the cell cycle, transcriptional changes, loss of apoptosis, abnormal cell growth, and tumor formation. Signaling through the HER-2 homodimer is inhibited by the monoclonal antibody trastuzumab; the presence of trastuzumab can also induce antibody-dependent cellular cytotoxicity and inhibit angiogenesis. In addition, lapatinib is a small molecule that inhibits HER-1 and HER-2 tyrosine kinase activities.

Abbreviations: HER, human epidermal growth factor; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase.

From Ahn ER, Vogel CL. Dual HER2-targeted approaches in HER2-positive breast cancer. *Breast Cancer Res Treat* 2012;131:371–381, with permission.

PHARMACODYNAMICS

Lapatinib is a potent inhibitor of both EGFR and HER-2, showing a 50% inhibitory concentration $<0.2 \mu\text{M}$ [20]. Relationships between lapatinib dose and antitumor response are difficult to assess and have not been extensively explored.

Tolerability is limited by diarrhea at the dose level of 500 mg twice daily [15].

ADVERSE REACTIONS

Rash and gastrointestinal adverse events like diarrhea and vomiting are frequently seen during therapy with lapatinib. In

most cases, symptoms are mild and do not result in discontinuation of the drug. However, in an open-label study, severe diarrhea compromised therapy in 9.7% of patients treated with lapatinib together with capecitabine [21].

CONTRAINDICATIONS OR SPECIAL PRECAUTIONS

Lapatinib is contraindicated in cases of hypersensitivity to the active substance or to any of the excipients [1]. Decreased left ventricular ejection fraction (LVEF) occurred in $\sim 1\%$ of patients receiving lapatinib and was asymptomatic in $>90\%$ of cases. It resolved in $\sim 70\%$ of patients, ei-

Table 1. Summary table

Generic name	Lapatinib ditosylate monohydrate
Chemical name	<i>N</i> -[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[(2-methylsulfonyl)ethylamino)methyl]-2-furyl] quinazolin-4-amine
Commercial names	Tyverb®, Tykerb®
Molecular weight (D)	581.06
Mechanism of action	Reversible inhibition of intracellular tyrosine kinase domain of EGFR and HER-2
Route of administration	Oral
Protein binding (%)	99
Metabolism	Major: CYP3A4 (70%); minor: CYP3A5, 2C19, and 2C8
Elimination	Primarily hepatic; <2% renal elimination
Terminal half-life	~24 hours after multiple dosing [8]
Main toxicities	Frequent: diarrhea, vomiting, rash; rare: decreased left ventricular function [1]
Unique features	Combined inhibition of both HER-2 and EGFR tyrosine kinases; convenient because of oral therapy
Main drug and CAM interactions	Strong CYP3A4 inhibitors (erythromycin, clarithromycin, itraconazole, ketoconazole, voriconazole) and inducers (carbamazepine, dexamethasone, phenytoin, phenobarbital, rifampicin, St. John's wort)
Dose adaptations	Moderate and severe liver impairment (Child-Pugh score, 7–9 or >9, respectively): ≥50% dose reduction of lapatinib should be considered
Abbreviations: CAM, complementary and alternative medicine; CYP, cytochrome P450; EGFR, epidermal growth factor receptor; HER-2, human epidermal growth factor receptor 2.	

ther with or without discontinuation of therapy [1]. In a phase I dose-escalation study, 81 patients received daily doses of lapatinib in the range of 175–1,800 mg/day. Thirteen of the 81 patients were found to have a corrected QT by the Friedericia method >480 msec. Analysis of the data suggested a relationship between lapatinib concentration and the QTc interval [22]. LVEF and QTc time should therefore be determined at initiation of therapy and also during treatment. Because of the association of treatment with lapatinib and the occurrence of interstitial lung disease and pneumonitis, physicians should be alert to pulmonary symptoms. Lapatinib should be discontinued when patients experience grade ≥3 pulmonary toxicity, manifested by severe dyspnea, cough, or fever. It is recommended that liver function tests (transaminases, bilirubin, and alkaline phosphatase) be assessed at initiation of therapy and monthly thereafter. Lapatinib should be at least temporarily discontinued if changes in serum liver function tests are severe [1].

EFFICACY

Lapatinib in Combination with Capecitabine in Patients with Advanced Breast Cancer or MBC

On April, 28, 2008, the European Medicines Agency (EMA) Committee for Medicinal Products for Human use (CHMP) granted conditional marketing authorization for lapatinib [23]. Sometimes, the CHMP recommends that a medicine be given “conditional approval.” This happens when the Committee based its positive opinion on data that, although not yet comprehensive, indicate that the medicine’s benefits outweigh its risks.

The registration of lapatinib was approved primarily based on a phase III, randomized, open-label study comparing lapatinib plus capecitabine with capecitabine alone in 324 patients with HER-2+ advanced breast cancer or MBC that had progressed during prior treatment with anthracyclines, taxanes, and trastuzumab. Patients were randomized to receive lapatinib at a dose of 1,250 mg/day continuously plus capecitabine at a dose of 2,000 mg/m² per day on days 1–14 of a 21-day cycle or capecitabine at a dose of 2,500 mg/m² per day on days 1–14 of a 21-day cycle alone. The primary endpoint was the TTP. Secondary endpoints included the OS time, RR, progression-free survival (PFS) interval, and tolerability. Inclusion of patients was prematurely discontinued because of a significant difference in TTP in favor of the combination therapy: at an interim analysis, the median TTP with combination therapy was 8.4 months, compared with 4.4 months with capecitabine alone (hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.34–0.71; *p* < .001). However, there was no significant difference in the median OS times found between the two groups [24]. At the time of closure of accrual, however, the difference in the TTP between groups was 50% lower, at 1.9 months (6.2 months versus 4.3 months; HR, 0.57; 95% CI, 0.43–0.77; *p* < .001). The OS duration did not differ significantly between groups (15.6 months versus 15.3 months; HR, 0.78; 95% CI, 0.55–1.12; *p* = .177) [25].

In the final analysis of mature survival data, including 90% of patients intended to receive capecitabine who had crossed over to the combination arm when enrollment was halted, the median OS time did not differ between groups (17.3 months versus 14.9 months; HR, 0.87; 95% CI, 0.71–1.08; *p* = .210).

However, the study design did not allow for drawing definite conclusions from the survival data [25].

Lapatinib in Combination with an Aromatase Inhibitor for Postmenopausal Women with HR⁺ HER-2⁺ MBC

In June 2010, the EMEA approved lapatinib in combination with an aromatase inhibitor for the first-line treatment of postmenopausal women with HR⁺ HER-2⁺ MBC [1]. In a double-blind, randomized, placebo-controlled trial comparing lapatinib at a dose of 1,500 mg/day continuously in combination with letrozole at a dose of 2.5 mg/day orally with letrozole alone, a significantly longer PFS interval (8.2 months versus 3.0 months) was demonstrated in MBC patients. However, at the time of analysis, when <50% of death events had been recorded, the median OS time in the lapatinib plus letrozole group (33.3 months) did not differ significantly from that of the letrozole plus placebo group (32.3 months; HR, 0.74; 95% CI, 0.5–1.1; $p = .113$) [27].

Off-Label Use of Lapatinib

Lapatinib in Combination with Trastuzumab Beyond Progression

In 296 MBC patients who were progressive on their latest trastuzumab-containing regimen, continuation of therapy with lapatinib at a dose of 1,000 mg daily combined with 2 mg/kg trastuzumab weekly was superior to lapatinib alone at a dose of 1,500 mg daily in terms of the PFS interval (HR, 0.73; 95% CI, 0.57–0.93; $p = .008$). The median OS time in patients receiving lapatinib plus trastuzumab did not differ significantly from that of patients receiving lapatinib monotherapy (51.6 weeks versus 39.0 weeks; HR, 0.75; 95% CI, 0.53–1.07; $p = .106$). Diarrhea occurred more frequently in the combination arm [28].

First-Line Paclitaxel in Combination with Lapatinib

Because of dual inhibition of EGFR and HER-2 by lapatinib, the efficacy of lapatinib for patients with HER-2⁺ and uncharacterized HER-2 MBC was investigated in a phase III, double-blind, randomized study. In 597 patients with MBC, the addition of lapatinib to first-line treatment with paclitaxel did not show any significant difference in terms of the TTP, event-free survival duration, or OS time, compared with treatment with paclitaxel alone. Diarrhea and rash occurred significantly more frequently in the combination group [29].

Lapatinib in Clinical Guidelines

A clinical guideline with recommendations on the treatment of patients with MBC was provided by the U.K. National Institute for Health and Clinical Excellence (NICE) [30]. Trastuzumab is only used in patients with HER-2⁺ tumors in combination with systemic chemotherapy. There is controversy about its use when chemotherapy is stopped when disease is progressive [30]. In a randomized, controlled trial in HER-2⁺ breast cancer patients who had progressed during treatment with trastu-

zumab, the continuation of trastuzumab (6 mg/kg 3-weekly) in combination with capecitabine led to a significantly longer TTP (8.2 months versus 5.6 months; unadjusted HR, 0.69; 95% CI, 0.48–0.97; two-sided log-rank $p = .0338$) and greater overall RR (48.1% versus 27.0%; odds ratio, 2.50; $p = .0115$) than with capecitabine alone [31]. The median OS time was not significantly different in the combination arm compared with the capecitabine arm (24.9 months and 20.6 months, respectively; HR, 0.94; 95% CI, 0.65–1.35; $p = .73$) [1, 32]. According to the recent NICE guideline, it is advised to discontinue trastuzumab when there is disease progression outside the CNS based on uncertainties in clinical effectiveness as well as cost-effectiveness [30].

When continuation of trastuzumab is not considered to be useful, lapatinib plus capecitabine could be an alternative for capecitabine or vinorelbine monotherapy. Although the combination of lapatinib with capecitabine resulted in a significantly longer TTP and PFS interval than with capecitabine monotherapy, the difference in the mean OS times was small and not significant [26]. Considering its small effect size and the impact of the use of lapatinib on National Health Services resources, NICE does not recommend the use of lapatinib in patients with HER-2⁺ MBC that has progressed following treatment with anthracyclines, taxanes, and trastuzumab, except in the context of clinical trials [33].

Clinical evidence from one study demonstrated that lapatinib with letrozole, compared with letrozole monotherapy, led to a longer PFS time in patients with HR⁺ HER-2⁺ MBC. However, no significant effect on the OS outcome was seen [27].

In an economic evaluation, the combination of lapatinib and letrozole was not cost-effective when compared with letrozole monotherapy [34].

Considering the lack of trials directly comparing lapatinib with trastuzumab, together with the small effect size of lapatinib when added to standard second-line agents, the U.K. and The Netherlands (personal communication, GlaxoSmithKline) do not reimburse for lapatinib in combination with capecitabine for the treatment of HER-2⁺ HR⁺ advanced breast cancer or MBC. Recently, in The Netherlands, on the basis of an indirect comparison, the Committee for Pharmaceutical Aid advised reimbursing for lapatinib in combination with an aromatase inhibitor for the indication of first-line treatment of HER-2⁺ HR⁺ MBC in patients with slowly progressing disease and without brain and extensive visceral metastases [35].

CONCLUSION, FUTURE DIRECTIONS, AND AREAS OF UNCERTAINTY

Lapatinib is a reversible inhibitor of both the EGFR and HER-2 tyrosine kinases approved (conditionally by the EMEA) for the treatment of HER-2⁺ advanced breast cancer or MBC. Lapatinib is moderately to well tolerated, with a low incidence of serious adverse events. However, when combined with capecitabine, diarrhea can be severe. Discussion remains about the efficacy of lapatinib in patients with MBC when combined with capecitabine, showing only a small difference in the TTP [24] without any significant difference in the OS

duration [25, 26], compared with treatment with capecitabine alone.

Because of the lack of published studies directly comparing trastuzumab with lapatinib (in combination with second-line agents) when disease has progressed, a sound evaluation of clinical effectiveness as well as cost-effectiveness is not possible.

At present, despite published data, it is uncertain whether or not lapatinib has a beneficial effect in the prevention and treatment of HER-2⁺ CNS metastases [36–38]. This is a subject of current trials [39].

Results of the NCT00667251 trial should reveal the efficacy of lapatinib with trastuzumab when added to taxane-based chemotherapy, followed by lapatinib or trastuzumab monotherapy, as first-line therapy for HER-2⁺ MBC patients [39].

The Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation (ALTTO) study is a randomized, open-label, multicenter phase III study comparing the activity of lapatinib alone with that of trastuzumab alone and with that of trastuzumab followed by lapatinib and with that of lapatinib concomitantly with trastuzumab in the adjuvant treatment of patients with HER-2-overexpressing breast cancer [40]. The Tykerb® Evaluation After Chemotherapy (TEACH) study is investigating whether or not lapatinib as maintenance therapy

after standard adjuvant therapy for HER-2⁺ early breast cancer will lead to a longer OS time [41].

Combining extracellular and intracellular blockage of HER-2 by trastuzumab and lapatinib, respectively, for early-stage breast cancer may be an interesting treatment strategy. Preliminary results of the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NEO-ALLTO) study [42], a randomized, open-label, multicenter, phase III study comparing the efficacy of neoadjuvant lapatinib plus paclitaxel with that of trastuzumab plus paclitaxel and with that of concomitant lapatinib and trastuzumab plus paclitaxel given as neoadjuvant treatment in HER-2/ErbB-2 overexpressing and/or amplified primary breast cancer, show higher pathological complete response and objective (clinical) response rates in the combination arm than with either trastuzumab or lapatinib alone [43].

Definitive results of these ongoing phase III studies are eagerly awaited in order to define the position of lapatinib in breast cancer treatment guidelines.

AUTHOR CONTRIBUTIONS

Conception/Design: Frans L. Opdam, Henk-Jan Guchelaar, Jan H.M. Schellens, Jos H. Beijnen

Data analysis and interpretation: Jan H.M. Schellens

Manuscript writing: Frans L. Opdam, Jan H.M. Schellens, Jos H. Beijnen

Final approval of manuscript: Frans L. Opdam, Henk-Jan Guchelaar, Jan H.M. Schellens, Jos H. Beijnen

REFERENCES

- European Medicines Agency. Tykerb® Summary of Product Characteristics. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000795/WC500044957.pdf, accessed July 20, 2011.
- U.S. Food and Drug Administration. Tykerb® Approval Letter 13–3–2007. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022059s000_APPROV.pdf, accessed July 20, 2011.
- U.S. Food and Drug Administration. Tykerb® Approval Letter 29–01–2010. Available at http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2010/022059s007ltr.pdf, accessed July 20, 2011.
- Pegram MD, Pauletti G, Slamon DJ. HER-2/neu as a predictive marker of response to breast cancer therapy. *Breast Cancer Res Treat* 1998;52:65–77.
- 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;344:783–792.
- Xia W, Mullin RJ, Keith BR et al. Anti-tumor activity of GW572016: A dual tyrosine kinase inhibitor blocks EGF activation of EGFR/erbB2 and downstream Erk1/2 and AKT pathways. *Oncogene* 2002;21:6255–6263.
- Ahn ER, Vogel CL. Dual HER2-targeted approaches in HER2-positive breast cancer. *Breast Cancer Res Treat* 2012;131:371–381.
- Xia W, Liu LH, Ho P et al. Truncated ErbB2 receptor (p95ErbB2) is regulated by heregulin through heterodimer formation with ErbB3 yet remains sensitive to the dual EGFR/ErbB2 kinase inhibitor GW572016. *Oncogene* 2004;23:646–653.
- Bai F, Freeman BB 3rd, Fraga CH et al. Determination of lapatinib (GW572016) in human plasma by liquid chromatography electrospray tandem mass spectrometry (LC-ESI-MS/MS). *J Chromatogr B Analyt Technol Biomed Life Sci* 2006;83:169–175.
- Burris HA 3rd, Hurwitz HI, Dees EC et al. Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. *J Clin Oncol* 2005;23:5305–5313.
- Koch KM, Reddy NJ, Cohen RB et al. Effects of food on the relative bioavailability of lapatinib in cancer patients. *J Clin Oncol* 2009;27:1191–1196.
- Medina PJ, Goodin S. Lapatinib: A dual inhibitor of human epidermal growth factor receptor tyrosine kinases. *Clin Ther* 2008;30:1426–1447.
- U.S. Food and Drug Administration. Tykerb®. Clinical Pharmacology and Biopharmaceutics NDA review. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022059s000_ClinPharmR.pdf, accessed February 1, 2012.
- Polli JW, Olson KL, Chism JP et al. An unexpected synergist role of P-glycoprotein and breast cancer resistance protein on the central nervous system penetration of the tyrosine kinase inhibitor lapatinib (N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2(methylsulfonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine; GW572016). *Drug Metab Dispos* 2009;37:439–442.
- Burris HA 3rd, Taylor CW, Jones SF et al. A phase I and pharmacokinetic study of oral lapatinib administered once or twice daily in patients with solid malignancies. *Clin Cancer Res* 2009;15:6702–6708.
- Teng WC, Oh JW, New LS et al. Mechanism-based inactivation of cytochrome P450 3A4 by lapatinib. *Mol Pharmacol* 2010;78:693–703.
- Midgley RS, Kerr DJ, Flaherty KT et al. A phase I and pharmacokinetic study of lapatinib in combination with infusional 5-fluorouracil, leucovorin and irinotecan. *Ann Oncol* 2007;18:2025–2029.
- Smith DA, Koch KM, Arya N et al. Effects of ketoconazole and carbamazepine on lapatinib pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2009;67:421–426.
- Kelly H, Graham M, Humes E et al. Delivery of a healthy baby after first-trimester maternal exposure to lapatinib. *Clin Breast Cancer* 2006;7:339–341.
- 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;64:6652–6659.
- Capri G, Chang J, Chen SC et al. An open-label expanded access study of lapatinib and capecitabine in patients with HER2-overexpressing locally advanced or metastatic breast cancer. *Ann Oncol* 2010;21:474–480.
- U.S. Food and Drug Administration Center for Drug Evaluation and Research. Medical Review Tykerb®. 6–3–2007. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022059s000_MedR_P1.pdf, accessed July 20, 2011.
- European Medicines Agency. Assessment Report for Tykerb®. Procedure No. EMEA/H/C/795, 2008. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/

- human/000795/WC500044960.pdf, accessed July 20, 2011.
24. Geyer CE, Forster J, Lindquist D et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355:2733–2743.
 25. 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;112:533–543.
 26. Cameron D, Casey M, Oliva C et al. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: Final survival analysis of a phase III randomized trial. *The Oncologist* 2010;15:924–934.
 27. Johnston S, Pippen J, Pivot X et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol* 2009;27:5538–5546.
 28. Blackwell KL, Burstein HJ, Storniolo AM et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol* 2010;28:1124–1130.
 29. Di Leo A, Gomez HL, Aziz Z et al. Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. *J Clin Oncol* 2008;26:5544–5552.
 30. National Institute for Health and Clinical Excellence (NICE). Advanced Breast Cancer: Diagnosis and Treatment. Available at <http://www.nice.org.uk/nicemedia/live/11778/43414/43414.pdf>, accessed July 20, 2011.
 31. von Minckwitz G, du Bois A, Schmidt M et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: A German Breast Group 26/Breast International Group 03–05 study. *J Clin Oncol* 2009;27:1999–2006.
 32. von Minckwitz G, Schwedler K, Schmidt M et al. Trastuzumab beyond progression: Overall survival analysis of the GBG 26/BIG 3–05 phase III study in HER2-positive breast cancer. *Eur J Cancer* 2011;47:2273–2281.
 33. National Institute for Health and Clinical Excellence (NICE). Final Appraisal Determination: Lapatinib for the Treatment of Women With Previously Treated Advanced or Metastatic Breast Cancer. Available at <http://www.nice.org.uk/nicemedia/live/11731/49197/49197.pdf>, accessed July 20, 2011.
 34. National Institute for Health and Clinical Excellence (NICE). Liverpool Review and Implementation Group. Lapatinib and Trastuzumab in Combination With an Aromatase Inhibitor for the First-Line Treatment of Metastatic Hormone Receptor Positive Breast Cancer Which Overexpresses HER-2. Available at <http://www.nice.org.uk/nicemedia/live/12337/52179/52179.pdf>, accessed July 20, 2011.
 35. CFH-Rapport 11/34: Lapatinib (Tyverb®) in Combinatie met een Aromataseremmer. Available at http://www.cvh.nl/binaries/live/cvzinternet/hst_content/nl/documenten/cfh-rapporten/2011/cfh1106-lapatinib-tyverb.pdf, accessed July 20, 2011.
 36. Clayton AJ, Danson S, Jolly S et al. Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. *Br J Cancer* 2004;91:639–643.
 37. Stemmler L, Kahlert S, Siekiera W et al. Brain metastases (BM) in patients treated with trastuzumab for HER2 overexpressing metastatic breast cancer (MBC): Incidence and survival. *J Clin Oncol* 2005;23:131S.
 38. Stemmler J, Schmitt M, Willems A et al. Brain metastases in HER2-overexpressing metastatic breast cancer: Comparative analysis of trastuzumab levels in serum and cerebrospinal fluid. *J Clin Oncol* 2006;24:64S.
 39. Johnston SRD, Gelmon KA, Pivot XB et al. Ongoing clinical development of lapatinib in HER2-positive (HER2+) metastatic breast cancer (MBC): An innovative approach to recruit patients in clinical studies. *J Clin Oncol* 2011;29(15 suppl):TPS105.
 40. ClinicalTrials.gov. ALTTO (Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation) Study; BIG 2–06/N063D. Available at <http://www.clinicaltrials.gov/ct2/show/NCT00490139?term=ALTTO&rank=1>, accessed July 20, 2011.
 41. ClinicalTrials.gov. Tykerb Evaluation After Chemotherapy (TEACH): Lapatinib Versus Placebo In Women With Early-Stage Breast Cancer. Available at <http://www.clinicaltrials.gov/ct2/show/NCT00374322?term=NCT00374322&rank=1>, accessed July 20, 2011.
 42. ClinicalTrials.gov. Neo ALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) Study. Available at <http://www.clinicaltrials.gov/ct2/show/NCT00553358?term=NEO-ALTTO&rank=1>, accessed July 20, 2011.
 43. Baselga J, Bardbury I, Eidtmann H et al. First Results of the NeoALTTO Trial (BIG 01–06 / EGF 106903): A phase III, randomized, open label, neoadjuvant study of lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2-positive primary breast cancer [abstract S3–3]. Presented at the San Antonio Breast Cancer Symposium, San Antonio, Texas, December 8–12, 2010.
 44. Wikipedia. Bestand:Lapatinib.svg. Available at <http://nl.wikipedia.org/wiki/Bestand:Lapatinib.svg>, accessed July 20, 2011.