Current and Future Roles of Lapatinib in HER2-Positive Breast Cancer

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In this article, we review the underlying biology and pharmacology behind lapatinib and summarize clinical trials with lapatinib. We also describe the ongoing clinical trials that use lapatinib as part of adjuvant and neoadjuvant therapy. These trials could change the standard of care in the next few years.

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(3) Demonstrate knowledge of and use the most optimal chemotherapy combinations with trastuzumab.

(4) Apply the knowledge of the current use of lapatinib in HER2-positive breast cancer.

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Dear Colleague:
This is the fourth and final E-Update in the series entitled HER1 and HER2 Targeting in Breast
Current and Future Roles of Lapatinib in HER2-Positive Breast Cancer

Cancer. This clinically focused update concerns current and future roles for lapatinib in the treatment of HER2-positive breast cancer. An HER2-targeted tyrosine kinase inhibitor, lapatinib is an important new drug in treating HER2-positive breast cancer patients who have had disease progression after trastuzumab-based therapy.

Dr. Cynthia Ma and Dr. Ron Bose, my colleagues at Washington University School of Medicine, review the underlying biology and pharmacology of lapatinib, including adverse effects and potential drug-drug interactions, and summarize key clinical trials. One of these trials led to FDA approval of lapatinib in combination with capecitabine for the treatment of advanced or metastatic HER2-positive breast cancer in patients who received prior therapy with an anthracycline, a taxane, and trastuzumab. Looking towards the future, Drs. Ma and Bose describe ongoing clinical trials that use lapatinib as part of adjuvant and neoadjuvant care and that could change the standard of care in a few years. Preclinical work is looking at identifying potential resistance mechanisms to lapatinib and developing strategies to overcome such resistance.

We hope that taken together, the four updates in this series focused on HER2-directed therapy will improve the clinician’s understanding of how to maximize the benefits of HER2 targeting in patients with breast cancer and minimize side effects and serious toxicities.

Sincerely,
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Introduction
HER2-positive breast cancer comprises approximately 25% of breast cancer cases and before trastuzumab (Herceptin) was available, this breast cancer subtype was associated with a poorer prognosis. Use of trastuzumab plus chemotherapy in either the metastatic or adjuvant disease settings has dramatically improved the clinical outcomes for HER2-positive patients. Disease progression after trastuzumab-based therapy, however, is a known clinical problem and the HER2-targeted tyrosine kinase inhibitor, lapatinib (TyKerb), is an important new drug for treating such patients. In this article, we review the underlying biology and pharmacology behind lapatinib and summarize clinical trials with lapatinib. We also describe the ongoing clinical trials that use lapatinib as part of adjuvant and neoadjuvant therapy. These trials could change the standard of care in the next few years.

Mechanism of Action
Lapatinib is a member of the 4-anilinoquinazoline class of tyrosine kinase inhibitors.[1] Other members of this class of drugs include erlotinib (Tarceva) and gefitinib (Iressa). All three compounds inhibit tyrosine kinases by binding to their ATP-binding site.

Lapatinib inhibits HER2 and its close family member, epidermal growth factor receptor (EGFR), with similar potency, whereas erlotinib and gefitinib show preferential inhibition of EGFR.[2] Upon binding to HER2, lapatinib inhibits tyrosine phosphorylation and turns off the oncogenic signal transduction pathways that arise from HER2.[3] Because lapatinib targets the tyrosine kinase domain, it is capable of also inhibiting a HER2 cleavage product, the p95-HER2 protein, which contains only the intracellular portion of HER2.[4]

Preclinical studies demonstrated that lapatinib can inhibit the growth of tumor cell lines that overexpress either HER2 or EGFR.[5] The mechanism of the growth inhibition involved cell cycle arrest in some cell lines and apoptosis of other lines. Furthermore, Slamon and colleagues showed that lapatinib could inhibit the growth of breast cancer cell lines that have been made resistant to trastuzumab by prolonged trastuzumab exposure in tissue culture.[6]

Clinical Pharmacology and Potential Adverse Effects
The recommended dose of lapatinib is 1,250 mg once daily and it should be taken either an hour before or after a meal.[7] Dose reduction should be considered in patients with severe hepatic dysfunction (Childs-Pugh Class C). The effective half-life of lapatinib is 24 hours.

Lapatinib is metabolized by CYP3A4, and this is the basis of potential drug-drug interactions with other compounds which inhibit or induce CYP3A4 (Table 1). Inducers of CYP3A4 may reduce the effectiveness of lapatinib, while inhibitors of CYP3A4 may increase drug toxicity by increasing the steady-state levels of lapatinib. Additionally, grapefruit juice and St. John’s wort can alter the metabolism of lapatinib and should be avoided.[7]

Common adverse effects of lapatinib include diarrhea and skin rash. Asymptomatic decrease in left ventricular ejection fraction (LVEF) may occur in 2% to 3% of patients. In these cases, lapatinib should be held for 2 weeks. Cautious restart of lapatinib at a dose of 1,000 mg was used in two women in a phase III clinical trial of lapatinib plus capecitabine, and this resulted in no recurrence of the LVEF decline.[8]

Another cardiac adverse effect that requires monitoring is QTc prolongation. Incidence of this is reported to be < 1%, but can be increased by concomitant use of certain fluoroquinolones (including ciprofloxacin [Cipro] and moxifloxacin [Avelox]), dolasetron (Anzemet), type Ia and type III antiarrhythmic drugs, and thioridazine (Mellaril).

Table 1. A Partial List of Inducers and Inhibitors of CYP3A4 [7]

(Comprehensive evaluation of potential drug-drug interactions should be performed by the physician prescribing lapatinib.)

<table>
<thead>
<tr>
<th>Inducers of CYP3A4</th>
<th>Inhibitors of CYP3A4</th>
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</thead>
<tbody>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Azole antifungals (ketoconazole [Nizoral], itraconazole [Sporanox], voriconazole [VFEND])</td>
</tr>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>Erythromycin, clarithromycin (Biaxin), and telithromycin (Ketek)</td>
</tr>
<tr>
<td>Dexamethasone (Decadron)</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>Nafcillin (Unipen, Nallpen)</td>
<td>Diclofenac (Cataflam, Voltaren)</td>
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<tr>
<td>Phenoobarbital</td>
<td>Imatinib (Gleevec)</td>
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<tr>
<td>Nevirapine (Viramune)</td>
<td>Isoniazid (Nyrazid)</td>
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<tr>
<td>Rifampin (Rifadin) and Rifabutin (Mycobutin)</td>
<td>Nefazodone (Serzone)</td>
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<td></td>
<td>Nicardipine (Cardene) and Verapamil, Quinidine, HIV protease inhibitors</td>
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Lapatinib Monotherapy

The antitumor effect of lapatinib in HER2-positive breast cancer was first suggested in phase I studies. In a phase I study of single agent lapatinib in 67 heavily pretreated patients with EGFR-expressing and/or HER2-overexpressing metastatic cancers, lapatinib induced a partial response (PR) in 4 patients with advanced breast cancer that progressed on prior trastuzumab.[8] All four patients had tumors that overexpressed HER2 (3+ by immunohistochemistry), three of which also coexpressed EGFR, and two patients had recurrent inflammatory breast cancer.

In another phase I study in patients with solid tumors, a PR was observed in a patient who had trastuzumab-resistant HER2-overexpressing breast cancer and received lapatinib at 1,600 mg/d, and a patient who had squamous cell carcinoma of the lung and received lapitinib at 900 mg/d.[9] In both studies, lapatinib was well tolerated at doses of 1,600 mg or lower once daily. The most frequently reported drug-related adverse events were diarrhea and rash. The median dose of lapatinib in the responders was 1,200 mg daily.

Subsequent phase II studies demonstrated that lapatinib is effective for the treatment of refractory HER2-positive breast cancer previously treated with trastuzumab. Burstein et al reported a multicenter phase II study of lapatinib monotherapy at 1,500 mg once daily in patients with
advanced breast cancer that progressed on prior anthracyclines, taxanes, and capecitabine (Xeloda). The study enrolled 140 patients with HER2-positive breast cancer previously treated with trastuzumab and 89 patients with HER2-negative disease. A response rate (RR) of 4.3% and a clinical benefit rate (progression free for ≥ 6 months) of 6% were observed in the HER2-positive cohort. No objective tumor responses occurred in the HER2-negative cohort. The results of this study indicate that HER2-positive breast cancers that develop resistance to trastuzumab may still retain sensitivity to lapatinib.

As frontline therapy for HER2-amplified advanced breast cancer, two administration schedules of lapatinib (500 mg twice daily and 1,500 mg once daily) were tested in a randomized, open-label, phase II trial involving 138 patients. No significant differences in efficacy or toxicity were found between the treatment arms. A RR of 24% and a 6-month progression-free survival (PFS) rate of 43% were observed. The response rate is similar to those observed for trastuzumab when used as first-line therapy for a similar population of women.

Lapatinib Combination Therapy for Metastatic Breast Cancer

Lapatinib in Combination With Capecitabine

Lapatinib in combination with capecitabine was compared with capecitabine alone in a phase III, randomized, open-label study in women with advanced HER2-positive advanced breast cancer who had previously been treated with an anthracycline, taxane, and trastuzumab. Patients were randomly assigned to receive either:

- combination therapy (lapatinib at a dose of 1,250 mg/d continuously plus capecitabine at a dose of 2,000 mg per square meter of body-surface area on days 1 through 14 of a 21-day cycle); or
- monotherapy (capecitabine alone at a dose of 2,500 mg per square meter on days 1 through 14 of a 21-day cycle).

The initial report from the planned interim analysis demonstrated that the addition of lapatinib significantly reduced the hazard for time to disease progression (8.4 vs 4.4 months, hazard ratio [HR] = 0.49; 95% confidence interval [CI] = 0.34-0.71; P < .001). There was also a trend toward fewer cases of central nervous system (CNS) disease progression in the combination arm (4 vs 11, P = .1). No increase in serious adverse events was seen with the addition of lapatinib. Based on this result, accrual to the trial was discontinued and cross-over was offered to women receiving monotherapy.

A follow-up analysis continues to demonstrate that the addition of lapatinib to capecitabine significantly improves time to progression (TTP) (HR = 0.57; 95% CI = 0.43-0.77; P < .001) and reduces the risk for progression in the CNS as a first event (4 vs 13, P = .045) without a substantive increase in toxicity. There is also a trend toward improved overall survival (HR = 0.78; 95% CI = 0.55-1.12; P = .177). The overall response rate (ORR) was 24% for patients receiving the combination and 14% for those treated with capecitabine alone (P = .017). Based on these results, lapatinib in combination with capecitabine was approved by the US Food and Drug Administration (FDA) in March 2007 for the treatment of advanced or metastatic HER2-positive breast cancer in patients who had received prior therapy with an anthracycline, a taxane, and trastuzumab.

Lapatinib in Combination With Paclitaxel

Lapatinib in combination with paclitaxel was tested in a randomized, double-blind phase III study as first-line treatment for patients with metastatic breast cancer, and the results were presented at the American Society of Clinical Oncology (ASCO) 2007 Annual Meeting. Five hundred and eighty patients were randomized to receive paclitaxel at 175 mg/m² intravenously every 3 weeks with either lapatinib at 1,500 mg or placebo orally daily. This trial was conducted in countries where HER2 testing was not routinely available and postenrollment, centralized HER2 testing was performed on the tumor biopsies.

The addition of lapatinib increased the incidence of diarrhea (all grades, 58% vs 26%; grade 3 or 4, ...
16% vs 1%), rash (44% vs 22%), and mucositis (13% vs 3%) (P < .0001). The combination arm had a higher response rate (35.1% vs 25.3%, P = .008) and clinical benefit rate (40.5% vs 31.9%, P = .025), although the TTP and event-free survival rates were similar for the overall study population. In the HER2-positive cohort, the addition of lapatinib resulted in a higher RR (60% vs 36%, P = .027) and TTP (8.1 vs 5.8 months, P = .011). This contrasts to the HER2-negative cohort, which did not derive any benefit from lapatinib. Treatment-related deaths were higher in the combination arm (2.7% vs 0.6%).

**Lapatinib in Combination With Trastuzumab for Combined HER2 Targeting Effect**

Combined HER2 therapy with lapatinib and trastuzumab was compared with lapatinib alone in a randomized phase III study in 296 heavily pretreated patients with HER2-positive metastatic breast cancer that progressed on trastuzumab therapy.[17] Patients were randomized to receive either the combination therapy (lapatinib at 1,000 mg daily plus trastuzumab at 2 mg/kg weekly after 4 mg/kg loading dose) or lapatinib at 1,500 mg daily. The combination therapy significantly improved PFS (12 vs 8.1 months, P = .008) and the clinical benefit rate, defined as complete response, partial response, and stable disease > 6 months (24.7% vs 12.4%, P = .01). Both study arms, however, had similar RR (10.3% vs 6.9%, P = .46) and OS (51.6 vs 39 weeks, P = .106). Seventy three patients crossed over to the combination arm after progression on lapatinib alone.

Both treatment regimens were generally well tolerated. Grade 1/2 diarrhea was higher in the combination arm (53% vs 41%), but grade 3 and 4 diarrhea occurred in only 7% of patients in both arms. Acneiform rash was more common in the lapatinib alone arm (29% vs 22%), likely due to higher lapatinib dose. Asymptomatic decline in LVEF (> 20% and below lower limits of normal) occurred in eight patients in the combination therapy arm and five patients in the lapatinib alone arm. One death occurred due to cardiac toxicity in the combination arm.

This study indicates that the combination of lapatinib and trastuzumab is tolerable and appears to be more effective than lapatinib monotherapy for trastuzumab refractory HER2-positive breast cancer. The potential benefit of combined HER2 targeted therapy is being actively evaluated in the ongoing adjuvant ALTT0 (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) trial (described in the Future Directions and Ongoing Clinical Trials section).

**Lapatinib in Inflammatory Breast Cancer**

The promising activity of lapatinib in inflammatory breast cancer (IBC) observed in phase I studies prompted further evaluation in phase II trials. In an open-label multicenter phase II trial of lapatinib in patients with recurrent or anthracycline-refractory IBC, HER2-positive patients were assigned to cohort A and HER2-negative/EGFR-positive patients were assigned to cohort B.[18] Forty-five patients (30 in cohort A; 15 in cohort B) received lapatinib at 1,500 mg once daily. Fifteen patients (50%) in cohort A had clinical responses, compared with only one patient in cohort B, indicating the selective activity of lapatinib for HER2-positive disease.

**Lapatinib in Brain Metastasis**

The trend towards fewer CNS metastases in the phase III trial of lapatinib plus capecitabine vs capecitabine alone has sparked interest in use of lapatinib to treat brain metastases from HER2-positive breast cancer.[8] In a prospective, multicenter, phase II study of lapatinib monotherapy (750 mg twice a day) in 39 women with HER2-positive breast cancer and brain metastases, 1 patient achieved a PR in the CNS by the Response Evaluation Criteria in Solid Tumors (RECIST), for a response rate of 2.6%. [19] Although the study did not meet the primary efficacy goal, which would have required at least four responders, volumetric reductions in CNS target lesions were observed in some patients. Three patients achieved at least 30% volumetric reductions in CNS target lesions, and an additional seven patients achieved reductions of 10% to 30%. In addition, there was a trend toward a longer TTP for patients with at least 30% volumetric reduction vs others (1.8 vs 5.4 months, P = .16). Similar results were seen when patients were dichotomized according to at least 10% volumetric reduction vs others (median TTP from 8-week MRI, 1.8 vs 3.5 months, P = .04).
The role of lapatinib in women with HER2–positive breast cancer and progressive CNS disease after cranial radiotherapy was further evaluated in an international study enrolling 241 patients and using volumetric changes as a primary endpoint.[20] Recently reported preliminary data from the initial 104 patients showed that 15 patients (6%) met volumetric criteria for partial response and 46 patients (19%) experienced ≥ 20% volume reduction of CNS disease. The median time to volume progression in these patients was 15.1 weeks (range 12–24 weeks) and the 6-month PFS rate was 22% (95% CI = 16%-28%). In the extension arm of the study, 16 of 40 patients (40%) treated with the combination of lapatinib and capetcitabine after either systemic or CNS disease progression on monotherapy lapatinib, experienced ≥ 20% volume reduction of CNS disease. Although overall lapatinib activity was modest and target response rate was not reached, some patients derived durable volumetric reduction in brain tumor burden, with improvement or stabilization of CNS symptoms.

Future Directions and Ongoing Clinical Trials

Lapatinib as Adjuvant Therapy

The use of lapatinib in the adjuvant setting is being evaluated in the ALTTO study (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization). ALTTO is an international study with a goal of enrolling 8,000 patients worldwide. The study is being conducted through the National Cancer Institute (NCI), Breast Cancer Intergroup, Breast International Group (BIG), and the North Central Cancer Treatment Group (NCCTG).

Patients with early stage HER2-positive breast cancer are randomized to one of four treatment arms:

- trastuzumab alone;
- lapatinib alone;
- trastuzumab followed by lapatinib; or
- lapatinib in combination with trastuzumab.

Patients receive study treatment for 1 year. Eligibility criteria include node-positive patients or node-negative patients with tumors ≥ 1 cm, and adequate surgical excision and axillary evaluation.

The ALTTO trial also has several molecular markers built into its trial design. The primary tumor is evaluated for the c-myc oncogene, the PTEN tumor suppressor, and the p95-HER2 protein, which is a cleavage product of HER2. Overexpression of c-myc is thought to sensitize HER2-positive tumors to trastuzumab. In contrast, tumors with loss of PTEN or increased p95-HER2 expression are likely to be better treated with lapatinib. Blood samples and additional tumor biopsies, where available, are being stored for studies of circulating tumor cells and proteomic markers.

The ALTTO trial was launched in May 2007, and the first patients were enrolled in June 2007. Enrollment is projected to continue till June 2010.

Lapatinib in Neoadjuvant Therapy

Several cooperative groups and academic centers have initiated neoadjuvant trials involving lapatinib, including BIG, the National Surgical Adjuvant Breast and Bowel Project (NSABP), and Baylor Breast Care Center. The NeoALTTO trial, sponsored by BIG, parallels the ALTTO trial. Patients receive concurrent neoadjuvant paclitaxel with a HER2 targeted therapy for 6 weeks. For the HER2 targeted therapy, patients are randomized to:

- weekly lapatinib at 1,500 mg daily;
- trastuzumab; or
- trastuzumab plus lapatinib at 1,000 mg daily.

Following the 6 weeks of neoadjuvant therapy, patients proceed to surgery and then adjuvant therapy with fluorouracil, epirubicin (Ellence), and cyclophosphamide (FEC) along with the same HER2 targeted therapy that they received preoperatively. Projected trial enrollment is 450 patients and the study started in November 2007.
Predictors of Lapatinib Response

Similar to trastuzumab, the benefit of lapatinib in breast cancer is limited to HER2-positive disease, and increased expression and activation status of HER2 are associated with response. PTEN deficiency and insulin-like growth factor I receptor (IGF-1R) expression have been associated with trastuzumab resistance, but do not appear to preclude response to lapatinib.

In the Burris phase I study of lapatinib monotherapy, sequential tumor biopsies from 33 patients, including the 4 patients with breast cancer who had PR, were examined for correlation with treatment response.[21] Clinical response was associated with an increased pretreatment expression of HER2, activated HER2 (p-ErbB2), increased EGFR ligand (transforming growth factor alpha) and a pretreatment score on the terminal deoxynucleotidyl transferase (TdT)-mediated biotinylated deoxyuridine-triphosphate (duTP)-biotin nick end-labeling (TUNEL) assay higher than 0. Tumor regression was associated with increased tumor cell apoptosis. Interestingly, elevated IGF-1R and p70 S6 kinase, which have been linked to resistance to trastuzumab, are associated with treatment response.

The lapatinib phase II first-line trial evaluated correlations between baseline tumor biomarker expression levels and clinical response to lapatinib.[22] For the initial 65 patient samples analyzed, an elevation of HER2 expression, by quantitative reverse transcription polymerase chain reaction (QRT-PCR), was significantly associated with response to treatment with lapatinib (P = .02) and a longer time to progression (P < .0025). In addition, increased HER3 expression is associated with prolonged PFS. No association was observed with ERBB4, PTEN, and c-myc in this preliminary analysis. Gene expression pattern analysis performed on 33 samples with high quality RNA demonstrated that lapatinib responders exhibited increased expression of genes involved in the PI3Kinase, transforming growth factor beta (TGF-b), and vascular endothelial growth factor (VEGF) pathways and decreased expression of genes involved in the epidermal growth factor (EGF), platelet derived growth factor (PDGF), and apoptotic pathways.[22]

Tumor specimens were also evaluated in the phase II study of lapatinib in inflammatory breast cancer.[18] Within cohort A (HER2-positive cohort), phosphorylated HER3 and lack of p53 expression predicted response to lapatinib (P < .05). Tumors coexpressing pHER2 and pHER3 were more likely to respond to lapatinib (9 of 10 vs 4 of 14, P = .0045). PTEN deficiency, which has been associated with resistance to trastuzumab monotherapy, did not preclude response to lapatinib.

In addition, coexpression of IGF-1R, which has also been associated with trastuzumab resistance, did not affect the likelihood of response to lapatinib. PTEN loss in cell lines does not induce resistance in vitro to lapatinib.[23] Lapatinib blocks the transactivation of EGFR and HER2 by IGF-1R, and this provides an explanation as to why IGF-1R coexpression does not preclude response to lapatinib in HER2-positive inflammatory breast cancer.[24]

Resistance to Lapatinib

Several potential resistance mechanisms to lapatinib have been described in laboratory-based experiments. A genetic screen for HER2 mutations that could produce resistance to lapatinib identified 12 HER2 kinase domain mutations including T798I.[25] HER2 T798I is homologous to EGFR T790M and ABL T315I mutations, which cause resistance to gefitinib and imatinib (Gleevec), respectively. Secondly, lapatinib treatment of a HER2-positive breast cancer cell line resulted in activation of estrogen receptor dependent gene expression, raising concerns that enhanced estrogen signaling may be a way for tumor cells to survive lapatinib treatment.[26] Combining lapatinib treatment with fulvestrant (Faslodex) reduced the rate of lapatinib resistance in this cell culture model.

Finally, lapatinib may be a substrate for the multidrug resistance protein, P-glycoprotein (P-gp), and breast tumors which express P-gp could simultaneously become resistant to both lapatinib and multiple cytotoxic chemotherapy drugs.[27] The extent to which these mechanisms will impact
clinical oncology remains to be seen. The duration of response to lapatinib in the initial monotherapy trials was sometimes short[9] and therefore, clinicians should be aware of the potential for drug resistance. Strategies to overcome such resistance are in preclinical development. Future research should clarify how frequently lapatinib resistance will be seen and how best to address it.

**Conclusion**

Lapatinib represents an important addition to the treatment of HER2-positive breast cancer. Its use in metastatic breast cancer that has previously treated with trastuzumab has been established and ongoing trials are evaluating its use in early stage breast cancer and in brain metastases.

**Key Points**

- HER2-positive breast cancers that progress on or after trastuzumab therapy frequently retain sensitivity to lapatinib.
- Lapatinib is FDA-approved for use in combination with capecitabine for the treatment of advanced or metastatic HER2-positive breast cancer in patients who had previously received an anthracycline, taxane, and trastuzumab.
- A trend towards lower rates of progressive CNS metastases was seen in the phase III clinical trial of lapatinib plus capecitabine. Clinical trials examining the use of lapatinib in the treatment of brain metastases are ongoing.
- Large, multicenter clinical trials of lapatinib in the adjuvant and neoadjuvant setting were started in 2007. Enrollment of eligible patients onto these trials should be encouraged.
- Mechanisms of resistance to lapatinib have been described in the laboratory. Their incidence and clinical impact on patients remains to be determined.

**References**


