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Phase II Trial of Lapatinib for Brain Metastases in Patients With Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer

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Abstract

Purpose—One third of women with advanced human epidermal growth factor receptor 2 (HER-2)–positive breast cancer develop brain metastases; a subset progress in the CNS despite standard approaches. Medical therapies for refractory brain metastases are neither well-studied nor

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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established. We evaluated the safety and efficacy of lapatinib, an oral inhibitor of epidermal growth factor receptor (EGFR) and HER-2, in patients with HER-2–positive brain metastases.

Patients and Methods—Patients had HER-2–positive breast cancer, progressive brain metastases, prior trastuzumab treatment, and at least one measurable metastatic brain lesion. Patients received lapatinib 750 mg orally twice a day. Tumor response was assessed by magnetic resonance imaging every 8 weeks. The primary end point was objective response (complete response [CR] plus partial response [PR]) in the CNS by Response Evaluation Criteria in Solid Tumors (RECIST). Secondary end points included objective response in non-CNS sites, time to progression, overall survival, and toxicity.

Results—Thirty-nine patients were enrolled. All patients had developed brain metastases while receiving trastuzumab; 37 had progressed after prior radiation. One patient achieved a PR in the brain by RECIST (objective response rate 2.6%, 95% conditional CI, 0.21% to 26%). Seven patients (18%) were progression free in both CNS and non-CNS sites at 16 weeks. Exploratory analyses identified additional patients with some degree of volumetric reduction in brain tumor burden. The most common adverse events (AEs) were diarrhea (grade 3, 21%) and fatigue (grade 3, 15%).

Conclusion—The study did not meet the predefined criteria for antitumor activity in highly refractory patients with HER-2–positive brain metastases. Because of the volumetric changes observed in our exploratory analysis, further studies are underway utilizing volumetric changes as a primary end point.

INTRODUCTION

Amplification of human epidermal growth factor receptor 2 (HER-2) occurs in approximately 25% of breast carcinomas and has historically been associated with poorer disease-free and overall survival.[1] Over time, approximately one third of women treated with trastuzumab for advanced cancer will develop brain metastases.[2–5] Although trastuzumab reduces the risk of distant relapse in patients with HER-2–positive, early-stage breast cancer, the CNS remains a site of initial and subsequent relapse.[6] These and other data suggest that trastuzumab has limited penetration through the blood-brain barrier.[7]

Despite the use of whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS), a substantial percentage of patients with HER-2–positive, metastatic breast cancer succumb from progressive cancer within the CNS.[2] At present, there is no consensus about the appropriate medical therapy to offer patients with breast cancer whose brain metastases have progressed after radiotherapy. Retrospective case series and case reports have been published, but few chemotherapeutic agents have been prospectively evaluated in the breast cancer population.[4,8–11]

Lapatinib is a small-molecule inhibitor of epidermal growth factor receptor (EGFR) and HER-2.[12] In heavily pretreated patients, lapatinib achieved an investigator-reported objective response rate of 5% to 8% for systemic metastatic disease.[13] Objective responses in the CNS have been observed with gefitinib, a structurally similar compound, in patients with brain metastases from non–small-cell lung cancer (NSCLC).[14,15] Although neither gefitinib nor lapatinib cross the intact blood-brain barrier to a significant degree in pre-

clinical models, the blood-tumor barrier may be more permissive, leading to the hypothesis that lapatinib may have activity in established CNS disease.[16,17]

We conducted a phase II study to evaluate the clinical efficacy and adverse-effect profile of lapatinib in the treatment of women with brain metastases from HER-2–positive breast cancer. On the basis of the activity of lapatinib in refractory breast cancer, and its structural similarity to gefitinib, we hypothesized that lapatinib would be active in women with HER-2–positive breast cancer metastatic to the brain. This report summarizes the clinical outcomes of the study.

PATIENTS AND METHODS

Eligibility

Patients were required to be at least 18 years of age, provide written informed consent, and have HER-2–positive breast cancer, defined as 3+ immunohistochemistry or evidence of gene amplification by fluorescence in situ hybridization. Prior trastuzumab was required. Patients were eligible if they had documented CNS progression after WBRT, SRS, or both. Patients were also eligible if they had not previously received radiation therapy, provided that they were asymptomatic.

Eligible patients had at least one measurable lesion in the brain (defined as any lesion ≥ 1.0 cm in longest dimension), an Eastern Cooperative Oncology Group performance status 0 to 2, life expectancy ≥ 12 weeks, the ability to swallow oral medications, and the absence of a prior malignancy besides breast cancer unless treated with curative intent. Patients were required to have a left ventricular ejection fraction (LVEF) within institutional normal limits, absolute neutrophil count of at least 1,000/μL, platelet count of at least 75,000/μL, bilirubin no more than 1.5× upper limit of normal (ULN), AST and ALT no more than 5× ULN, and creatinine clearance of at least 25 mL/min. Patients with leptomeningeal carcinomatosis as the only site of CNS involvement were excluded.

All radiotherapy, chemotherapy, and/or hormonal therapy had to be completed at least 2 weeks before protocol treatment. Concurrent administration of other antineoplastic agents was not permitted. Patients were excluded from taking inducers or inhibitors of CYP3A4, including phenytoin. Corticosteroids were permitted.

This study was conducted in accordance with guidelines established by the United States Department of Health and Human Services. The National Cancer Institute Cancer Therapy Evaluation Program and institutional review boards of Dana-Farber Cancer Institute/Harvard Cancer Center (Boston, MA), University of North Carolina at Chapel Hill (Chapel Hill, NC), and Georgetown University (Washington, DC) approved the study. Patients were enrolled between September 2004 and September 2005.

Treatment Plan

The starting dose of lapatinib was 750 mg twice daily administered orally in continuous 4-week cycles. Lapatinib dose was held, then reduced to 500 mg twice a day and subsequently

to 1,250 mg once daily, for initial or recurrent grade 3 to 4 toxicity, or clinically significant grade 2 toxicity.

LVEF was measured every 8 weeks with a radioventriculogram or echocardiogram. Those with grade 3 or 4 left ventricular systolic dysfunction were taken off protocol. Patients with confirmed grade 3 or 4 interstitial pneumonitis were also taken off protocol.

Study Analysis

Patients were assessed for toxicity according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI-CTCAE v. 3.0). Staging procedures were completed every 8 weeks and included brain magnetic resonance imaging (MRI) and computed tomography (CT) scans of the chest, abdomen, and pelvis. MRI scans were performed using 3-mm slices for axial T1-weighted, contrast-enhanced images, and 5-mm slices for the other sequences. Patients continued study treatment until they withdrew consent, experienced unacceptable toxicity, or had progressive disease (PD).

The primary end point was objective response(complete response[CR]plus partial response [PR]) in the CNS. All measurable lesions, up to a maximum of five target lesions, were assessed. CNS responses were classified according to modified Response Evaluation Criteria in Solid Tumors (RECIST). CR was defined as the disappearance of all target and nontarget lesions. PR was defined as at least a 30% decrease in the sum longest dimension (LD) of target lesions *and* an absolute decrease of at least 5 mm in at least one target lesion. PD was defined as at least a 20% increase in the sum LD of target lesions *and* an absolute increase in size of at least 5 mm in at least one target lesion, *or* the appearance of one or more new lesions of at least 6 mm in size. Non-CNS response was assessed by RECIST (CR, disappearance of all measurable and nonmeasurable disease; PR, ≥30% decrease in sum LD of target lesions; PD, ≥20% increase in sum LD of target lesions). Date of progression was recorded as the first documented progression at any site (either CNS or non-CNS), as assessed by the local investigator. Patients were considered to have progressed if they were taken off study for clinical deterioration or died as a result of any cause, regardless of whether there was documented radiographic evidence of progression.

Evaluation of CNS lesions for response categorization was performed centrally at the Tumor Imaging Metrics Core of Dana-Farber/Harvard Cancer Center. For RECIST, images were transferred to a Voxar imaging workstation (Barco, Kortrijk, Belgium), where target lesions were measured using a linear digital caliper tool.

For volumetric analyses, MRI scans were transmitted to a Vitrea2 workstation (Vital Images, Minnetonka, MN). The contrast-enhancing portions of the target lesions were outlined across all MRI image slices in which the lesion appeared, and edited manually to fit the exact perimeter. The software calculated the tumor volumes by multiplying the outlined area by the slice thickness, and then by adding values across slices.

Patients were accrued in a two-stage design. The accrual goal was 37 patients (n =12, first stage; n =25, second stage); at least one CNS response was required in the first 12 patients to proceed to full accrual. The protocol-stipulated criteria indicated that four responders among

37 patients would be considered adequate to justify further study. With this study design, the trial had a 90% chance of positive findings if the true response rate was 20%, and a 10% chance of positive findings if the true response rate was 5%. Calculation of CIs was performed according to the Atkinson and Brown procedure.[18] Time-to-event variables were summarized using the Kaplan-Meier method. The point-wise confidence curves for time-to-event variables were generated using the Greenwood formula. The estimation of the median and its CI was as described by Therneau and Grambsch.[19] Comparison of time-to-event variables between subgroups was performed using the log-rank test.

RESULTS

Patients and Treatment Characteristics

A CNS response was observed in the third patient enrolled onto the study; hence the study proceeded to full accrual. Thirty-nine women were enrolled (two more than the accrual goal because they had already consented to enter the study when the 37th patient was registered). Table 1 lists the clinical characteristics of these women. All but two patients had experienced progression after CNS-directed radiation therapy. Among patients who had previously been irradiated, median time from last radiotherapy was 5.97 months. Patients received a median of two prior trastuzumab-containing chemotherapy regimens.

At the time of study analysis, 136 4-week cycles of treatment had been administered. Fifteen patients (38%) required at least one dose reduction, most commonly for diarrhea. Seventy-four percent of cycles were administered at full dose. In 23% of cycles, lapatinib dose was reduced to 500 mg twice a day. One patient required a further dose reduction to 1,250 mg once daily.

Toxicity

All patients were assessable for toxicity. The worst grades of treatment-related toxicity are listed in Table 2. The most common adverse event was diarrhea, which improved with supportive measures and/or dose reductions in most cases.

Three patients were removed from study because of toxicity. One patient experienced grade 3 elevation of transaminases; one patient experienced grade 3 diarrhea and anorexia; and one patient developed endocarditis, which was ultimately judged unlikely to be related to lapatinib.

One patient died suddenly while receiving her third cycle of lapatinib. Restaging studies performed after cycle 2 had demonstrated stable disease. The research staff spoke with the patient the day before her death and she reported feeling well, with the exception of a mild headache. An autopsy was declined, and the cause of death is unknown.

Cardiac Surveillance and Cardiotoxicity

No patient developed symptomatic congestive heart failure on study. Four patients developed asymptomatic declines in LVEF to less than 50% (range, 44% to 49%). Of the four patients, only one experienced a 10% or greater decline in LVEF from baseline. In two patients, lapatinib was continued per protocol, and repeat evaluation demonstrated

normalization of LVEF. One patient was taken off study after two cycles because of PD, and was lost to follow-up before reevaluation of LVEF. One patient died of an acute intracerebral hemorrhage 2 weeks after the last dose of study drug, before repeat cardiac evaluation. The event was judged related to anticoagulation with low molecular-weight heparin and warfarin for a pulmonary embolus in the setting of progressive CNS disease.

Efficacy

The principal end point of the study was the rate of CNS response by RECIST. Of 39 patients, one achieved a PR, for an overall CNS response rate of 2.6% (95% conditional CI, 0.21% to 26%; Fig 1; Table 3). This patient had received her last radiotherapy 12.6 months before study entry and did not require corticosteroids during the study period.

Sixteen patients (41%) had measurable non-CNS disease at baseline. Four (25%) achieved a PR in non-CNS sites (Table 4). Of the patients that responded in non-CNS sites, all were eventually taken off study for CNS progression. The relatively small proportion of patients with measurable non-CNS disease likely reflects that the study attracted a group of patients whose dominant problem was CNS progression.

Time to progression (TTP) and overall survival are shown in Figure 2. Median TTP was 3.0 months (95% CI, 2.3 to 3.7 months). For the patient with CNS objective response, TTP was 11.3 months. Seven patients (18%) were free of any progression at 16 weeks. One additional patient had stable CNS disease at 16 weeks, but progressed in her adrenal lesions. Of these patients, three received corticosteroids at some point during the study. Two patients sustained temporary increases in corticosteroid dose beginning during cycle 1 of therapy, but which subsequently decreased, and one patient had a sustained decrease in steroid dose from baseline.

At the time of this final study analysis, all patients had completed protocol-directed therapy. Patients were removed from the study for PD in the CNS only (n =24), PD in non-CNS sites only (n =4), PD in both CNS and non-CNS sites (n =5), toxicity (n =3), death (n =1), or other (n =2; physician-patient decision and generalized clinical deterioration, respectively).

Volumetric Analysis of CNS Lesions

An exploratory analysis was conducted of volumetric changes in CNS target lesions. For this analysis, 34 of 39 patients were included. Of the remaining five patients, one patient was excluded because of technical problems that did not allow calculation of lesion volumes, and four were excluded because they were taken off study before the week 8 evaluation.

Figure 3 illustrates the best volumetric change among the 34 patients who were included in the analysis. Three patients achieved at least 30% volumetric reductions in CNS target lesions, and an additional seven patients achieved reductions of 10% to 30%. It is not known what cutoff of volumetric change is clinically significant. We therefore conducted an exploratory analysis to correlate volumetric change and TTP. To avoid bias, we employed a “landmark method,” restricting the analysis to patients who had a follow-up MRI at 8 weeks and no progression before or at that time point (n =27). Patients with at least a certain

percentage of volumetric reduction at the 8-week point were compared with patients with lesser or no reduction at 8 weeks in terms of TTP from the end of 8 weeks (rather than from protocol entry). We found a trend toward a longer TTP for patientswith at least 30% volumetric reduction versus others (median TTP from 8-week MRI, 1.8 *v* 5.4 months; *P* =. 16). Similar results were seen when patients were dichotomized according to at least 10% volumetric reduction versus others (median TTP from 8-week MRI, 1.8 *v* 3.5 months; *P* =. 04).

DISCUSSION

In this prospective, multicenter, phase II study, we evaluated the safety and efficacy of lapatinib in women with HER-2–positive breast cancer and brain metastases. One patient achieved a PR in the CNS by RECIST, for a response rate of 2.6%. The study did not meet the primary efficacy goal, which would have required at least four responders. However, we did observe volumetric reductions in CNS target lesions in some patients. On the basis, in part, of results from this study, a large, international study was initiated to further evaluate the role of lapatinib monotherapy in women with HER-2–positive breast cancer and progressive CNS disease after cranial radiotherapy.[20] This study will utilize volumetric changes as a primary end point.

The CNS response rate in this study was similar to that observed for lapatinib for systemic disease in phase II studies of trastuzumab-refractory patients.[21,22] In a phase III study evaluating capecitabine versus capecitabine plus lapatinib in women with metastatic disease, the addition of lapatinib led to a statistically significant improvement in TTP, and numerically fewer patients experienced CNS progression.[23] Given these data, and past data demonstrating improvements in response rate when cytotoxic agents are added to trastuzumab (compared with trastuzumab monotherapy), future studies of lapatinib for CNS disease should include an evaluation of lapatinib combined with cytotoxic agents with the potential to cross the blood-tumor barrier.[24–26] Lapatinib could also be evaluated with cranial radiotherapy, on the basis of preclinical data indicating that lapatinib may act as a radiosensitizer.[27] Studies of lapatinib in less refractory patients or studies to determine whether the agent can prevent the appearance of CNS disease may also be of interest.

Our study had several limitations. First, we cannot exclude the possibility that CNS penetration of lapatinib was suboptimal. Indeed, since the study was initiated, a high incidence of CNS-only recurrence in non–small-cell lung cancer patients with an initial response to therapy to gefitinib has been reported.[28–30] In designing the trial, we chose the dosing schedule on the basis of pharmacokinetic data indicating that the same total daily dose, when divided twice a day, leads to approximately twice the area under the curve compared with a once daily schedule.[31] As in any phase II trial, our results apply only to the dose and schedule that were used. Further optimization of lapatinib dose was outside the scope of this trial. However, the rate of grade 3 diarrhea was higher in this study compared with other trials of lapatinib, which supports the pharmacokinetic data.[32] In phase I studies, dose-limiting toxicity was reached at 900 mg twice a day; therefore, from a practical standpoint, we do not believe the dose could be further escalated without a corresponding increase in toxicity.[33]

Another limitation was the choice of CNS response criteria. We prospectively developed modified RECIST to evaluate CNS response, but acknowledge that these are not the standard neurooncology criteria. In a patient population with limited options, we did not want to take patients off study for small changes in size that could be in the range of interobserver variation, and therefore required a 5-mm absolute change in the size of at least one CNS target lesion, in addition to standard RECIST. Conversely, we aimed to be more conservative in ascertaining response (for example, a patient with a single target lesion measuring 10 mm would be required to have shrinkage to 5 mm or less to qualify as a PR [ie, >30% decrease in LD and at least 5 mm absolute change]). Volumetric measurements may ultimately provide a more accurate estimate of tumor burden; however, it is unclear what degree of volumetric change is clinically significant.[21,34,35] In this study, there was a suggestion of clinical benefit, as ascertained by longer TTP, associated with volumetric changes of at least 10%. This hypothesis could be tested prospectively in future trials, as in trials of biologic agents, TTP may be a more relevant end point than objective response.

Although we believe that the absence of progression at 16 weeks in 18% of patients is suggestive of clinical benefit, we are not aware of any studies in which patients with progressive CNS disease are followed with imaging studies without treatment. Without an untreated reference population, we cannot make any definite conclusions. Of note, the median time from last radiation to study entry was 5.9 months, and patients were required to have progressive CNS disease for study entry. Therefore, we do not believe that the stabilizations that were observed were a result of prior radiation.

In conclusion, to our knowledge, this is the first prospective study evaluating a targeted agent for the treatment of brain metastases in patients with HER-2–positive breast cancer. Results of this study have led to a multicenter phase II trial of lapatinib in patients with HER-2–positive brain metastases, and studies of lapatinib in combination with cytotoxic agents are being initiated. This trial also underscores the feasibility of medical oncology treatment trials for brain metastases, and the urgent need to identify new treatment approaches for patients with CNS involvement, particularly for patients with HER-2–positive disease.

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References

1. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987; 235:177–182. [PubMed: 3798106]

2. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer. 2003; 97:2972–2977. [PubMed: 12784331]
3. 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. [PubMed: 15266327]
4. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. J Clin Oncol. 2004; 22:3608–3617. [PubMed: 15337811]
5. Lin NU, Winer EP. Brain metastases: The HER2 paradigm. Clin Cancer Res. 2007; 13:1648–1655. [PubMed: 17363517]
6. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005; 353:1673–1684. [PubMed: 16236738]
7. Pestalozzi BC, Brignoli S. Trastuzumab in CSF. J Clin Oncol. 2000; 18:2349–2351. [PubMed: 10829059]
8. Boogerd W, Dalesio O, Bais EM, et al. Response of brain metastases from breast cancer to systemic chemotherapy. Cancer. 1992; 69:972–980. [PubMed: 1735089]
9. Trudeau ME, Crump M, Charpentier D, et al. Temozolomide in metastatic breast cancer (MBC): A phase II trial of the National Cancer Institute of Canada - Clinical Trials Group (NCIC-CTG). Ann Oncol. 2006; 17:952–956. [PubMed: 16565212]
10. Rivera E, Meyers C, Groves M, et al. Phase I study of capecitabine in combination with temozolomide in the treatment of patients with brain metastases from breast carcinoma. Cancer. 2006; 107:1348–1354. [PubMed: 16909414]
11. Oberhoff C, Kieback DG, Wurstlein R, et al. Effectiveness and tolerance of primary topotecan chemotherapy in patients with breast cancer and brain metastases: Results of a pilot study. Proc Am Soc Clin Oncol. 20:72b, 2001. (abstr 2036).
12. 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. [PubMed: 12214266]
13. Burstein, HJ.; Storniolo, AM.; Salazar, VM., et al. A phase II, open-label, multicenter study of lapatinib (GW572016) in two cohorts of patients with advanced or metastatic breast cancer who have progressed while receiving trastuzumab-containing regimens: Interim analysis. Presented at the 29th Annual Congress of the European Society for Medical Oncology; October 29–November 2, 2004; Vienna, Austria.
14. Katz A, Zalewski P. Quality-of-life benefits and evidence of antitumour activity for patients with brain metastases treated with gefitinib. Br J Cancer. 2003; 89(suppl):S15–S18. [PubMed: 14661048]
15. Ceresoli GL, Cappuzzo F, Gregorc V, et al. Gefitinib in patients with brain metastases from non-small-cell lung cancer: A prospective trial. Ann Oncol. 2004; 15:1042–1047. [PubMed: 15205197]
16. Stewart DJ, Mikhael NZ, Nair RC, et al. Platinum concentrations in human autopsy tumor samples. Am J Clin Oncol. 1988; 11:152–158. [PubMed: 3358362]
17. Stewart DJ, Molepo JM, Green RM, et al. Factors affecting platinum concentrations in human surgical tumour specimens after cisplatin. Br J Cancer. 1995; 71:598–604. [PubMed: 7880744]
18. Atkinson EN, Brown BW. Confidence limits for probability of response in multistage phase II clinical trials. Biometrics. 1985; 41:741–744. [PubMed: 4074823]
19. Therneau, TM.; Grambsch, PM. Modeling Survival Data. New York, NY: Springer; 2000.
20. Lin NU, Dieras V, Paul D, et al. EGF105084, a phase II study of lapatinib for brain metastases in patients (pts) with HER2+ breast cancer following trastuzumab (H) based systemic therapy and cranial radiotherapy (RT). J Clin Oncol. 2007; 25:35s. (suppl; abstr 1012).
21. Blackwell KL, Kaplan EH, Franco SX, et al. A phase II, open-label, multicenter study of GW572016 in patients with trastuzumab-refractory metastatic breast cancer. J Clin Oncol. 2004; 22:196s. (suppl; abstr 3006).
22. Blackwell KL, Burstein HJ, Pegram M, et al. Determining relevant biomarkers from tissue and serum that may predict response to single agent lapatinib in trastuzumab refractory metastatic breast cancer. J Clin Oncol. 2005; 23:193s. (suppl; abstr 3004).

23. 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. [PubMed: 17192538]
24. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 2002; 20:719–726. [PubMed: 11821453]
25. 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. [PubMed: 11248153]
26. Burstein HJ, Harris LN, Marcom PK, et al. Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: Multicenter phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm. J Clin Oncol. 2003; 21:2889–2895. [PubMed: 12885806]
27. Zhou H, Kim YS, Peletier A, et al. Effects of the EGFR/HER2 kinase inhibitor GW572016 on EGFR- and HER2-overexpressing breast cancer cell line proliferation, radiosensitization, and resistance. Int J Radiat Oncol Biol Phys. 2004; 58:344–352. [PubMed: 14751502]
28. Omuro AM, Kris MG, Miller VA, et al. High incidence of disease recurrence in the brain and leptomeninges in patients with nonsmall cell lung carcinoma after response to gefitinib. Cancer. 2005; 103:2344–2348. [PubMed: 15844174]
29. Namba Y, Kijima T, Yokota S, et al. Gefitinib in patients with brain metastases from non-small-cell lung cancer: Review of 15 clinical cases. Clin Lung Cancer. 2004; 6:123–128. [PubMed: 15476598]
30. Jackman DM, Holmes AJ, Lindeman N, et al. Response and resistance in a non-small-cell lung cancer patient with an epidermal growth factor receptor mutation and leptomeningeal metastases treated with high-dose gefitinib. J Clin Oncol. 2006; 24:4517–4520. [PubMed: 16983123]
31. Nativg, B.; Paul, E.; Koch, K., et al. GW572016 Investigator's Brochure, version 5. Upper Providence, PA: GlaxoSmithKline; 2005. p. 75
32. Gomez HL, Chavez MA, Doval DC, et al. A Phase II, randomized trial using the small molecule tyrosine kinase inhibitor lapatinib as a first-line treatment in patients with FISH-positive advanced or metastatic breast cancer. J Clin Oncol. 2005; 23:203s. (suppl; abstr 3046).
33. Burris HA, Taylor C, Jones SE, et al. A phase I study of GW572016 in patients with solid tumors. Proc Am Soc Clin Oncol. 2003; 22:248. (abstr 994).
34. Miranpuri SS, Schulz CA, Chappell RJ, et al. Comparison of methods for response analysis of central nervous system neoplasms. J Radiosurg. 2004; 2:153–161.
35. Kilpatrick MR, Lin NU, Smith JK, et al. Superiority of bi-dimensional measurements compared to RECIST in measuring response of metastatic brain tumors. J Clin Oncol. 2006; 24:68s. (suppl; abstr 1542).

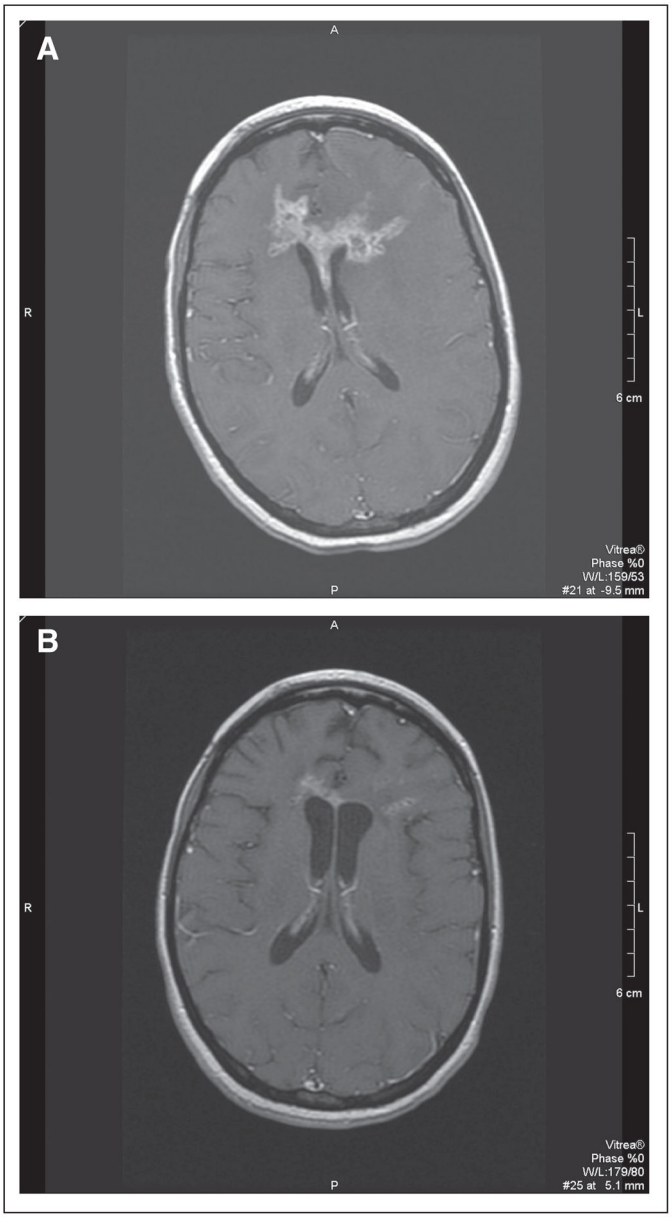

Fig 1.

Partial regression of CNS metastases after 16 weeks of lapatinib treatment. Representative image of patient with biopsy-proven CNS metastasis (A) before initiation of lapatinib and (B) after 16 weeks of lapatinib treatment demonstrating durable partial regression.

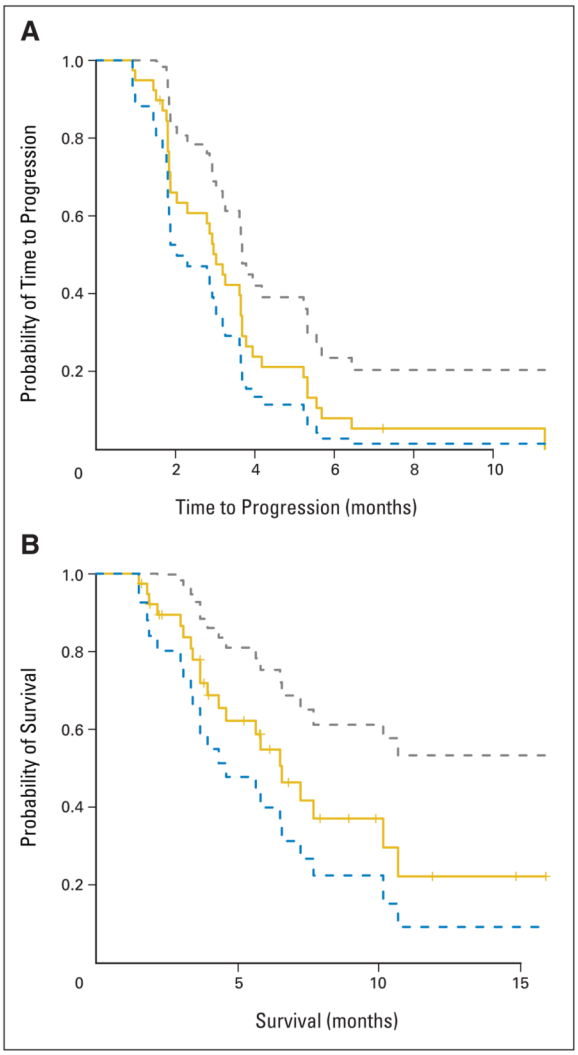

Fig 2.

(A) Proportion of patients without progression. Progression in either CNS or non-CNS sites is counted as progressive disease. Dashed lines indicate the upper and lower bounds of the 95% CI. (B) Overall survival for all 39 patients, from time of study entry. Dashed lines indicate the upper and lower bounds of the 95% CI.

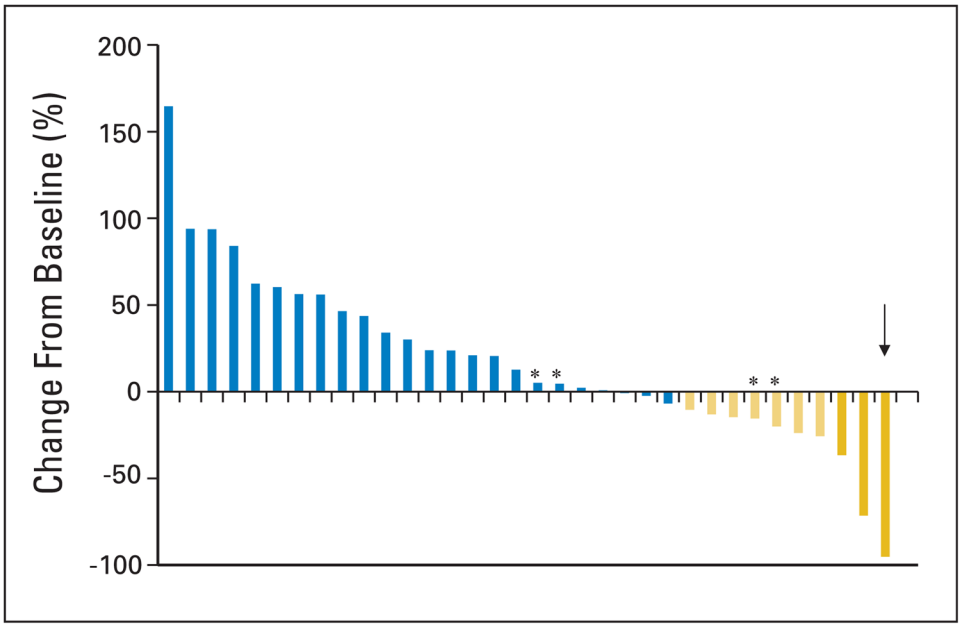

Fig 3.

Best volumetric change in sum of CNS target lesions with lapatinib. Each bar represents an individual patient with at least a baseline and week 8 magnetic resonance imaging scan (n = 34). Pale yellow bars indicate patients with 10% to 30% volumetric reduction. Yellow bars indicate patients with at least 30% volumetric reduction. The arrow denotes the patient who achieved a partial response in the CNS by Response Evaluation Criteria in Solid Tumors. (*) Concomitant increase in corticosteroid dose at the time of the restaging scan.

Table 1

Patient Characteristics

Characteristic	No. of Patients	%
Age, years		
Median	52	
Range	31–76	
ECOG performance status		
0	9	23
1	22	56
2	8	21
No. of sites of disease		
Median	3	
Range	2–6	
Sites of disease		
CNS	39	100
Lung or pleura	19	49
Liver	24	62
Bone	18	46
Breast/chest wall	5	13
Other	17	44
Estrogen-receptor status		
Positive	17	44
Negative	22	56
HER status		
IHC 3+, FISH not performed	28	72
IHC 2+, FISH-positive	3	8
FISH-positive, IHC not performed	1	2
Both IHC 3+ and FISH-positive	7	18
No. of prior chemotherapy regimens (adjuvant plus metastatic)		
1	5	13
2	6	15
≥3	28	72
No. of prior trastuzumab plus chemotherapy regimens		
1	14	36
2	14	36
≥3	11	28
Types of prior chemotherapy exposure		
Trastuzumab	39	100

Characteristic	No. of Patients	%
Taxane	35	90
Anthracycline	26	67
Vinorelbine	25	64
Capecitabine	15	38
Platinum	13	33
Temozolomide	5	13
Other	15	38
Prior CNS radiation		
None	2	5
WBRT only	20	51
SRS only	6	15
Both WBRT and SRS	11	28

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER-2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; WBRT, whole-brain radiotherapy; SRS, stereotactic radiosurgery.

Table 2

Worst Grade of Toxicity on Study (N =39)

	%		
Toxicity	**Grade 2**	**Grade 3**	**Grade 4**
Diarrhea	23	21	0
Fatigue	15	15	0
Headache	8	10	0
Rash	10	5	0
Anorexia	8	3	0
AST/ALT	5	8	0
Nausea	5	3	0

NOTE. Frequency of treatment-related toxicity according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, worst grade per patient.

Table 3

Overall CNS Activity Rate for Lapatinib

	Response	
Clinical Category	**No.**	**%**
Overall response	1	2.6
Complete response	0	0
Partial response	1	2.6
Stable disease ≥16 weeks (in both CNS and non-CNS sites)	6	15.4

Table 4

Overall Non-CNS Activity Rate for Lapatinib

Clinical Category	No. of Patients
Measurable disease	16
Overall response	4
Complete response	0
Partial response	4
Nonmeasurable disease	23

NOTE. Patients were not required to have measurable non-CNS disease to enter onto the study.