Multicenter Phase II Study of Lapatinib in Patients with Brain Metastases from HER2-Positive Breast Cancer

Nancy U. Lin,[1] Véronique Diéras,[2] Devchand Paul,[3] Dominique Lossignol,[4] Christos Christodoulou,[5] Hans-Joachim Stemmler,[6] Henri Roché,[7] Minetta C. Liu,[8] Richard Greil,[9] Eva Ciruelos,[10] Sibylle Loibl,[11] Stefania Gori,[12] Andrew Wardley,[13] Denise Yardley,[14] Adam Brufsky,[15] Joanne L. Blum,[16] Stephen D. Rubin,[17] Bernie Dharan,[17] Klaudia Steplewski,[17] Denise Zembryki,[17] Cristina Oliva,[18] Debasish Roychowdhury,[17] Paolo Paoletti,[17] and Eric P. Winer[1]

Abstract

Purpose: Brain metastases develop in one third of patients with advanced HER2+ breast cancer. Effective therapy for patients with central nervous system (CNS) progression after cranial radiation is extremely limited and represents a major clinical challenge. Lapatinib, an epidermal growth factor receptor/HER2 inhibitor, was associated with regressions of CNS lesions in a small phase 2 trial. The current study was done to further evaluate the CNS activity of lapatinib. The study was later amended to allow patients who progressed on lapatinib the option of receiving lapatinib plus capecitabine.

Experimental Design: Eligible patients had HER2+ breast cancer, progressive brain metastases, prior trastuzumab, and cranial radiotherapy. The primary end point was CNS objective response, defined as ≥50% volumetric reduction of CNS lesion(s) in the absence of increasing steroid use, progressive neurologic signs and symptoms, or progressive extra-CNS disease.

Results: Two-hundred and forty-two patients entered the study. CNS objective responses to lapatinib were observed in 6% of patients. In an exploratory analysis, 21% of patients experienced a ≥20% volumetric reduction in their CNS lesions. An association was observed between volumetric reduction and improvement in progression-free survival and neurologic signs and symptoms. Of the 50 evaluable patients who entered the lapatinib plus capecitabine extension, 20% experienced a CNS objective response and 40% experienced a ≥20% volumetric reduction in their CNS lesions.

Conclusions: This study confirms the modest CNS antitumor activity of lapatinib. Additional responses were observed with the combination of lapatinib and capecitabine. Further studies of lapatinib-based regimens for CNS metastases from HER2+ breast cancer are warranted.

Brain metastases are diagnosed in approximately one third of women treated with trastuzumab for advanced HER2+ breast cancer (1–5). The high incidence of HER2+ central nervous system (CNS) disease likely results from the inability of trastuzumab to cross the blood-brain barrier, in combination with a predilection of breast cancers that overexpress HER2 to metastasize to visceral sites, including the brain (6–9). Despite initial therapy with whole-brain radiotherapy or stereotactic

Authors' Affiliations: [1]Dana-Farber Cancer Institute, Boston Massachusetts, [2]Institut Curie, Paris, France, [3]Rocky Mountain Cancer Centers and U.S. Oncology, Denver, Colorado, [4]Institut Jules Bordet, Brussels, Belgium, [5]Metropolitan Hospital, Athens, Greece, [6]Klinikum der Universität München, Munich, Germany, [7]Institut Claudius Regaud, Toulouse, France, [8]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, [9]Private Medical University Hospital Salzburg, Salzburg, Austria, [10]Hospital 12 De Octubre, Madrid, Spain, [11]Klinikum der J.W. Goethe-Universitaet, Frankfurt, Germany, [12]Azienda Opsedaliera di Perugia, Perugia, Italy, [13]Christie Hospital NHS Foundation Trust, Manchester, United Kingdom, [14]Sarah Cannon Cancer Center, Nashville, Tennessee, [15]University of Pittsburgh, Magee Women's Hospital, Pittsburgh, Pennsylvania, [16]Baylor-Sammons Cancer Center, Texas Oncology, U.S. Oncology Research, Dallas, Texas, [17]GlaxoSmithKline, Upper Providence, Pennsylvania, and [18]GlaxoSmithKline, Stockley Park, United Kingdom

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This study was designed by both the academic investigators and employees of the sponsor. Data collection and analysis were supervised by an employee of the sponsor and reviewed along with the raw data by both academic investigators and employees of the sponsor. Interpretation of the data was performed by the academic investigators in conjunction with employees of the sponsor. The authors reviewed the results of the analyses, contributed to the writing of the manuscript, and were involved in the decision to submit the manuscript for publication.

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Requests for reprints: Eric P. Winer, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115. Phone: 617-632-3800; Fax: 617-632-1930; E-mail: ewiner@partners.org.

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Translational Relevance

Approximately one third of women with advanced HER2+ breast cancer will go on to develop brain metastases. Despite the prevalence of brain metastases in this patient population, effective therapy for patients with central nervous system (CNS) progression after cranial radiation remains extremely limited and represents a major clinical challenge. As the survival of patients with HER2+ breast cancer continues to improve, the need for effective salvage therapies after cranial radiotherapy will only increase.

This study enrolled more than 240 patients with progressive HER2+ brain metastases after cranial radiotherapy and trastuzumab. To our knowledge, it is the largest prospective study conducted to date evaluating systemic therapy for patients with brain metastases from breast cancer, which underscores the feasibility of conducting medical oncology treatment trials in this population. We observed a CNS objective response rate of 6% to lapatinib. In an exploratory analysis, 21% of patients achieved at least a 20% reduction in the volume of their CNS lesions. Additional responses were documented in patients who joined an optional extension phase of the study and who were treated with lapatinib plus capecitabine after progression on lapatinib alone. Based on these data, further studies of targeted therapy for brain metastases are warranted and ongoing.

radiosurgery, a substantial proportion of patients die of neurologic causes rather than of progressive extracranial disease (1). The development of effective systemic therapy for recurrent brain metastases remains a major challenge and an urgent medical need.

Lapatinib is a small-molecule tyrosine kinase inhibitor that inhibits the epidermal growth factor receptor and HER2. In a BALB/c nude mouse model, lapatinib inhibits the colonization of a brain-seeking derivative of the human MDA-MB-231 (231BR) cell line overexpressing both epidermal growth factor receptor and HER2 (10). In mice with established brain metastases, treatment with lapatinib also results in a statistically significant decrease in phosphorylated HER2, suggesting that pharmacologically relevant levels are achieved in CNS metastatic lesions (10).

Modest single-agent activity with lapatinib was observed in a pilot study of 39 women with progressive brain metastases from HER2+ breast cancer (11). Lapatinib combined with capecitabine increased the response rate and resulted in a statistically significant improvement in time to progression as compared with single-agent capecitabine in a phase III study of patients with refractory HER2+ metastatic breast cancer (12). In an exploratory analysis of this study, fewer CNS-progression events were observed in patients treated with lapatinib plus capecitabine compared with those treated with capecitabine alone.

The current study, EGF105084, was conducted to evaluate the activity of lapatinib in patients with progressive brain metastases from HER2+ breast cancer following prior trastuzumab and cranial radiotherapy. After release of the results of the phase III capecitabine plus lapatinib trial described above, EGF105084 was amended to allow patients, whose disease progressed on single-agent lapatinib, the option to receive the combination of lapatinib plus capecitabine.

Materials and Methods

Patients. Patients were enrolled from 63 centers between December 2005 and January 2007 and assigned to one of two cohorts: cohort A—Eastern Cooperative Group performance status (PS) 0 to 1 and 1 or 2 prior trastuzumab regimens; cohort B—Eastern Cooperative Group PS 2 and/or >2 prior trastuzumab regimens.

Patients were eligible if they had HER2+ breast cancer (defined as 3+ immunohistochemistry or evidence of gene amplification by fluorescence *in situ* hybridization) and unequivocal evidence of new and/or progressive brain metastases after completion of whole-brain radiotherapy or stereotactic radiosurgery. At least one brain lesion needed to be measurable (≥10 mm on T1-weighted, gadolinium-enhanced magnetic resonance imaging). Prior treatment with trastuzumab was also required. Additional inclusion criteria included age, ≥18 years, life expectancy of ≥12 weeks, left ventricular ejection fraction within the institution's reference range, and adequate hematologic, renal, and hepatic function. All radiotherapy, chemotherapy, and/or hormonal therapy had to be completed at least 2 weeks before protocol treatment. Concurrent administration of other antineoplastic agents, radiotherapy, or inducers or inhibitors of CYP3A4 were not permitted. Concomitant treatment with corticosteroids was permitted. Patients with leptomeningeal metastases as the only site of CNS involvement were excluded. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, in accordance with the Declaration of Helsinki. The institutional review board for each participating institution approved the study protocol. All patients gave written informed consent. The trial was registered at the ClinicalTrials.gov web site[19] (no. NCT00263588).

Study design. This was an open-label, phase II study. The primary end point was CNS objective response. Secondary end points included safety and tolerability, neurologic signs and symptoms (NSS), progression-free survival (PFS), and overall survival.

Administration of study treatment. The starting dose of single-agent lapatinib was 750 mg twice daily (b.i.d.). Dose delays of up to 2 weeks and two dose reductions, first to 1,500 mg once daily (q.d.) and second to 1,250 mg q.d., were allowed for treatment-related toxicities.

When the study first opened, patients with extra-CNS progression but stable or responsive CNS disease were given the option of enrolling into the extension phase and to receive lapatinib in combination with other systemic therapy until disease progression or withdrawal. In June 2006, the study was later amended to allow patients with radiographically documented CNS progression the option to continue to receive lapatinib in combination with capecitabine. During the extension phase, capecitabine was administered at 1,000 mg/m^2 b.i.d. for 14 days in each 21-day cycle in combination with lapatinib 1,250 mg q.d. One dose reduction was allowed for capecitabine (750 mg/m^2 b.i.d.) or lapatinib (1,000 mg/d).

Efficacy assessments. Brain magnetic resonance images were obtained every 8 weeks and included T1-weighted, contrast-enhanced images at 3.0 mm slice thickness without gaps in the axial dimension. All brain magnetic resonance images were evaluated by central, independent review according to previously described methods (11). Lesions previously treated with stereotactic radiosurgery were excluded as target lesions. A CNS objective response was defined as either a complete response or partial response (≥50% reduction in the volumetric sum of all measurable CNS lesions), provided there was no progression of extra-CNS disease, increasing steroid requirements, or worsening of NSS. Progressive disease was defined as the occurrence

[19] http://www.clinicaltrials.gov/

of any of the following: ≥40% increase in the volumetric sum of all evaluable CNS lesions relative to the nadir, new CNS lesions, progression of nonmeasurable CNS lesions, tumor-related increase in steroid dose, new or worsening tumor-related NSS, or progression of extra-CNS disease.

Neurologic exam was assessed at baseline and every 4 weeks. A physician-reported NSS worksheet was developed for the purpose of this study (Supplemental Fig. S1). The worksheet was derived from 13 adverse events selected from the literature (13) and measured by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI CTCAE v3.0), and grouped into seven categories, the details of which are found in the supplementary information.

The response to lapatinib outside of the CNS was evaluated by the investigator according to Response Evaluation Criteria in Solid Tumors guidelines, based on magnetic resonance imaging or computed tomography scans of the chest, abdomen, and pelvis obtained every 8 weeks.

Safety assessments. Adverse events were assessed every 4 weeks and graded according to NCI CTCAE v3.0. Serious adverse events were defined according to International Conference on Harmonization Good Clinical Practice guidelines. Left ventricular ejection fraction was assessed by echocardiogram or multigated acquisition scan every 8 weeks.

Statistical analysis. The null hypothesis was that the true CNS objective response rate for single-agent lapatinib was ≤10%; the alternative hypothesis was that the true CNS objective response rate was ≥20%. A total enrollment of 220 patients (110 per cohort) was planned (α level, 5%; power, 91%). Each cohort was evaluated separately. If there were 17 or more patients in a cohort with a CNS objective response, then the null hypothesis would be rejected. There was no prespecified hypothesis for the extension phase.

The modified intent-to-treat population was the primary population for the analysis of efficacy data and was prospectively defined as all patients who received at least four doses of the study medication and had measurable brain metastases at baseline. The intent-to-treat population was defined as all patients who received at least one dose of the study medication and was used to analyze safety data. CNS objective response rate and improvement in NSS were summarized using the exact 95% confidence interval (CI). PFS and overall survival were summarized by the Kaplan-Meier method. Exploratory analysis of PFS based on patients who had ≥20% volumetric reduction and patients who had ≥50% volumetric reduction was done using the Kaplan-Meier method and Cox regression. All *P* values were two-sided.

Results

Patient characteristics

Table 1 lists the characteristics of the patients included in the study. In total, 242 patients were enrolled in the intent-to-treat population (95 in cohort A and 147 in cohort B). The protocol-stipulated accrual goal was 110 patients per cohort; however, the final cohort assignment was made after central review of treatment history and before any analysis, resulting in some patients being reassigned to a different cohort and leading to the observed imbalance between cohorts. All patients received prior trastuzumab and cranial radiotherapy. Only 16 patients (7%) had completed cranial radiotherapy within 3 months of protocol entry; 71% of patients had received radiotherapy at least 6 months prior to study entry. At baseline, 211 (87%) patients had detectable extra-CNS metastatic disease, of which 130 had measurable extra-CNS disease, as defined by Response Evaluation Criteria in Solid Tumors guidelines.

Fifty-one patients received lapatinib plus capecitabine during the extension phase. Of these, three patients experienced only extra-CNS disease progression while on lapatinib monotherapy. One patient was excluded from CNS objective response analysis because of lack of volumetric data.

Delivered therapy

Disease progression was the most common reason for study medication discontinuation (74%). The median duration of exposure to lapatinib monotherapy was 84 days (range, 1-336 days).

Thirty patients (12%) required an initial dose modification from 750 mg b.i.d. to 1,500 mg q.d., and 14 patients (6%) required a second dose modification to 1,250 mg q.d. Fifty (21%) patients required dose delays. The majority of dose delays and reductions were the result of nonhematologic toxicity.

Toxicity

Lapatinib was generally well tolerated in this patient population (Table 2). The most common adverse events were diarrhea (65%), rash (30%), nausea (26%), and vomiting (24%). The most common grade 3 adverse event was diarrhea (13%), and two patients (<1%) experienced grade 4 diarrhea. A total of 17 patients (7%) had serious or non–serious adverse events that led to withdrawal from the study. Diarrhea was the only adverse event that led to withdrawal in more than one patient (two patients). One fatal serious adverse event was reported in a patient who expired 3 days after initiating lapatinib in the setting of high-dose opioids for pain.

The most common adverse events reported with the combination of lapatinib plus capecitabine were palmar-plantar erythrodysesthesia (45%), diarrhea (37%), and nausea (29%). Palmar-plantar erythrodysesthesia (8%), nausea (8%), vomiting (6%), and diarrhea (4%) constituted the most common grade 3 adverse events. One fatal serious adverse event was reported in a patient who died of a small intestinal perforation deemed by the treating physician as unrelated to lapatinib plus capecitabine.

Lapatinib monotherapy

Objective response rate. The CNS objective response rate was 6% in both cohorts (Table 3). A total of 15 partial responses and no complete responses were seen. There was no statistically significant difference in the rate of objective response according to the presence or absence of corticosteroid use at baseline, hormone receptor status, or time from last prior cranial radiotherapy.

PFS. Among the 237 patients in the modified intent-to-treat population, 215 (91%) experienced CNS and/or extra-CNS disease progression or died by the time of analysis. The median PFS was 2.4 months (Table 3). The percentage of patients without disease progression at 2, 4, and 6 months was 53.5% (95% CI, 47.1-59.9), 14.7% (95% CI, 10.1-19.3), and 5.9% (95% CI, 2.2, 9.6), respectively. There was no statistically significant difference in PFS according to the presence or absence of corticosteroid use at baseline, hormone receptor status, or time from last prior cranial radiotherapy.

The maximal volumetric change of CNS lesions was available for 200 patients and is illustrated in Fig. 1. There were 19 (8%) patients who experienced a ≥50% volumetric reduction in their CNS lesions. The median PFS was longer in these 19 patients compared with the rest of the study population: 3.38 months

versus 2.07 months, respectively. A trend toward a lower risk of disease progression or death was observed in these patients relative to the rest of the population [hazard ratio (HR), 0.61; 95% CI, 0.37-1.01; Table 4].

There were a total of 50 (21%) patients who experienced a ≥20% volumetric reduction in their CNS lesions. A lower risk of disease progression or death was also observed in patients with a ≥20% CNS volumetric reduction relative to the rest of the population (HR, 0.51; 95% CI, 0.36-0.72); therefore, the cutoff of ≥20% CNS tumor volume reduction seems to predict PFS benefit at least as well as a cutoff of ≥50% volumetric reduction (Table 4).

Site(s) of first progression. A total of 172 (73%) patients experienced disease progression. The initial site of disease

Table 1. Demographics and baseline characteristics

	Cohort A (*n* = 95)	Cohort B (*n* = 147)	Total (*N* = 242)
Patient demographics			
Median age, y (range)	49.5 (29-77)	49 (27-87)	49 (27-87)
Race			
African American/African	3 (3)	4 (3)	7 (3)
Asian	8 (8)	9 (6)	17 (6)
White: White/Caucasian/European	83 (88)	129 (88)	212 (88)
Disease status			
Median time since first diagnosis of metastatic disease, d (range)	716 (102-3,796)	952 (79-4,452)	855 (79-4,452)
Disease stage at first diagnosis, *n* (%)			
0	0	4 (3)	4 (2)
I	17 (18)	18 (12)	35 (14)
IIa	21 (22)	29 (20)	50 (21)
IIb	17 (18)	32 (22)	49 (20)
IIIa	12 (13)	18 (12)	30 (12)
IIIb	2 (2)	17 (12)	19 (8)
IIIc	6 (6)	2 (1)	8 (3)
IV	20 (21)	26 (18)	46 (19)
Histology			
Histology at first diagnosis, *n* (%)			
Adenocarcinoma	12 (13)	30 (20)	42 (17)
Lobular invasive	6 (6)	7 (5)	13 (5)
Papillary	1 (1)	0	1 (<1)
Infiltrating ductal NOS	61 (64)	86 (59)	147 (61)
Other	15 (16)	24 (16)	39 (16)
Combined receptor status, *n* (%)			
ER+ and/or PR+	46 (48)	80 (54)	126 (52)
ER- and PR-	49 (52)	67 (46)	116 (48)
HER2 status—immunohistochemistry, *n* (%)			
2+	8 (8)	11 (7)	19 (8)
3+	82 (86)	129 (88)	211 (87)
Unknown	5 (5)	7 (5)	12 (5)
HER2 status—FISH, *n* (%)			
Not done	11 (12)	20 (14)	31 (13)
Positive	41 (43)	49 (33)	90 (37)
Negative	1 (1)	1 (<1)	2 (<1)
Unknown	42 (44)	77 (52)	119 (49)
Prior treatment			
Prior trastuzumab regimens, *n* (%)			
1 regimen	30 (32)	16 (11)	46 (19)
2 regimens	65 (68)	24 (16)	89 (37)
3 regimens	0	49 (32)	49 (20)
4 regimens	0	32 (22)	32 (13)
≥5 regimens	0	26 (18)	26 (11)
Prior chemotherapy	95 (100)	147 (100)	242 (100)
Prior hormonal therapy	40 (42)	69 (47)	109 (45)
Prior radiotherapy			
Prior WBRT	91 (96)	138 (94)	229 (95)
Prior SRS	25 (26)	39 (27)	64 (26)
Prior WBRT and SRS	21 (22)	30 (20)	51 (21)
ECOG PS, *n* (%)			
0	31 (33)	28 (19)	59 (24)
1	64 (67)	45 (31)	109 (45)
2	0	73 (50)	73 (30)
3	0	1 (<1)	1 (<1)

Abbreviations: NOS, not otherwise specified; ER, estrogen receptor; PR, progesterone receptor; FISH, fluorescence *in situ* hybridization; WBRT, whole-brain radiotherapy; SRS, stereotactic radiosurgery; ECOG PS, Eastern Cooperative Group performance status.

Table 2. Incidence of the six most common adverse events by maximum CTC toxicity grade regardless of relationship (lapatinib monotherapy)

	Patients, no. (%)			
Adverse events	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Total (*N* = 242)				
Diarrhea	65 (27)	61 (25)	30 (13)	2 (<1)
Rash	50 (21)	15 (6)	6 (3)	1 (<1)
Nausea	36 (15)	21 (9)	7 (3)	0
Vomiting	32 (13)	16 (7)	9 (4)	0
Fatigue	27 (11)	19 (8)	6 (3)	0
Headache	28 (12)	13 (6)	4 (2)	0

Abbreviation: CTC, National Cancer Institute Common Terminology Criteria.

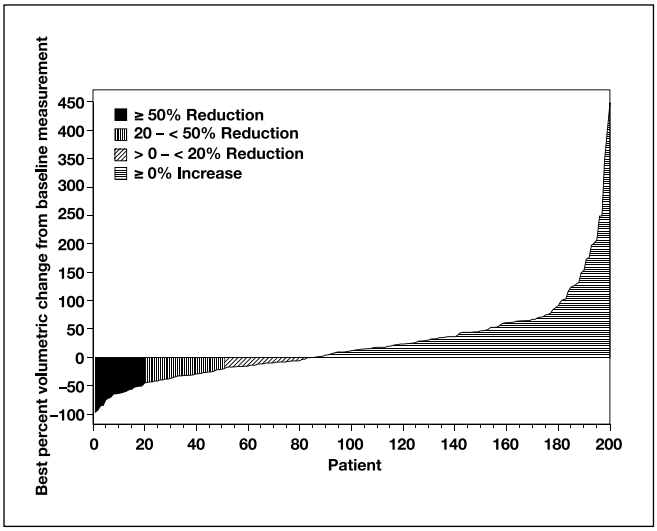

Fig. 1. Best percentage CNS volumetric change from baseline.

progression in 66% of patients overall was in the CNS, with or without extra-CNS disease progression. Only 16 (7%) patients experienced disease progression exclusively outside of the CNS.

Improvement in NSS. Criteria for improvement in NSS required a decrease by one or more grades from baseline of any tumor-related NSS, with confirmation at least 4 weeks later and no development or worsening in tumor-related NSS during this interval, radiographic CNS or extra-CNS disease progression, or increase in steroid requirement. Improvement in any non–tumor-associated NSS did not constitute an improvement in NSS. Of 198 patients with NSS at baseline, improvement was reported in 11.6% of patients (95% CI, 7.5-16.9) at week 8 on lapatinib. The most common NSS reported as improved were dizziness (6 patients), ataxia or headache (7 patients each), visual problems or vertigo (4 patients each), cranial nerves or strength (3 patients each), and nausea, consciousness, or seizure (2 patients each), with 12 out of 23 patients having an improvement in two or more NSS. Improvement in NSS was reported in 22.9% of patients (8 out of 35) who experienced a ≥20% reduction in the volume of their CNS lesions. In contrast, only 7.3% of patients (9 out of 124) who did not experience a decrease in the volume of their CNS lesions were reported to have improvement in NSS.

Overall survival. In total, 110 (46%) patients had died by the time of the analysis. The median survival was 6.4 months. Cohort A had a longer median survival than cohort B (9.6 and 5.5 months, respectively; Table 3). The difference in median survival between the two cohorts seems to reflect the shorter median survival of patients in cohort B with a baseline PS 2 [3.42 months (95% CI, 2.9-4.7) for a baseline PS 2 and 9.1 months (95% CI, 6.4-12.6) for a baseline PS 0 or 1].

Extra-CNS response. The degree to which objective responses or decreases in tumor size in the CNS paralleled that of the extra-CNS, and vice versa, was examined; however, it should be noted that neither measurable nor progressive extra-CNS disease was required for study entry. Of the 130 patients with measurable extra-CNS disease at baseline, 19 (15%) experienced an objective response by Response Evaluation Criteria in Solid Tumors guidelines in those sites. Of these 19 patients, 3 experienced a CNS objective response, and 12 experienced a reduction in the volume of their CNS lesions. Conversely, of the 16 patients with at least a 50% volumetric reduction of CNS lesions and without steroid increase,

Table 3. Summary of efficacy for lapatinib monotherapy (MITT population)

	Cohort A (*n* = 94)	**Cohort B (*n* = 143)**	**Total (*N* = 237)**
Best overall response, *n* (%)*			
Complete response	0	0	0
Partial response	6 (6)	9 (6)	15 (6)
Stable disease	41 (44)	47 (33)	88 (37)
Progressive disease	39 (41)	69 (48)	108 (46)
Unknown	8 (9)	18 (13)	26 (11)
Response rate (complete response + partial response)†	6 (6)	9 (6)	15 (6)
Exact 95% CI	(2.4-13.4)	(2.9-11.6)	(3.6-10.2)
Median PFS, mo (95% CI)	2.73 (1.87-3.45)	2.07 (1.87-2.79)	2.40 (1.87-2.79)
Median survival, mo (95% CI)	9.56 (6.18-n/e)	5.49 (4.73-7.03)	6.37 (5.49-8.25)

Abbreviations: MITT, modified intent-to-treat; n/e, not estimable.
*Best response achieved during the study, starting from week 8 after study drug administration and until disease progression.
† A CNS objective response was defined as a ≥50% volumetric reduction in sum of CNS target lesions with no new or progressive CNS or extra-CNS lesions, no increases in tumor-related steroid requirements, and no worsening of neurologic signs or symptoms.

Table 4. PFS (subgroup analysis)

	Patients experiencing a ≥20% CNS volumetric reduction		Patients experiencing a ≥50% CNS volumetric reduction	
	Yes	No	Yes	No
Lapatinib monotherapy				
n	50	186	19	217
Median PFS, mo (95% CI)	3.61 (3.19-3.71)	1.87 (1.84-2.14)	3.38 (2.79-5.36)	2.07 (1.87-2.73)
PFS HR (95% CI)	0.51 (0.36-0.72)		0.61 (0.37-1.01)	
Lapatinib + capecitabine extension phase				
n	20	30	11	39
Median PFS, mo (95% CI)	4.60 (3.68-8.15)	1.89 (1.48-3.65)	6.21 (3.94-n/e)	3.12 (1.68-3.75)
PFS HR (95% CI)	0.34 (0.17-0.68)		0.33 (0.14-0.76)	

Abbreviation: n/e, not estimable.

9 patients had measurable extra-CNS disease at baseline; 3 of these 9 (33%) patients experienced an objective response according to Response Evaluation Criteria in Solid Tumors guidelines, and 6 of these 9 patients experienced a reduction in the size of extra-CNS lesions.

Lapatinib plus capecitabine combination

CNS objective response. Fifty patients opted to enter the lapatinib plus capecitabine extension phase of the study and had volumetric data available for central review. Ten of 50 patients (20%; 95% exact CI, 3.0-33.7) experienced a CNS objective response. All objective responses were classified as partial responses.

PFS. The median PFS for patients on lapatinib plus capecitabine was 3.65 months (95% CI, 2.43-4.37). The percentage of patients free of disease progression at 2, 4, and 6 months was 66.3% (95% CI, 53.2-79.4), 37.3% (95% CI, 23.8-50.9), and 19.7% (95% CI, 7.6-31.7), respectively.

Twenty-two percent of patients experienced ≥50% reduction in the volume of CNS lesions. The median PFS was 6.21 months for patients who experienced a ≥50% reduction in the volume of CNS lesions and 3.12 months for the remainder of the patients (HR, 0.33; 95% CI, 0.14-0.76; Table 4).

Forty percent of patients experienced ≥20% reduction in the volume of CNS lesions. The durability of regressions in CNS tumor volume for these 20 patients is shown in Fig. 2. The median PFS was 4.60 months for patients who experienced a ≥20% reduction in the volume of CNS lesions and 1.89 months for the remainder of the patients (HR, 0.34; 95% CI, 0.17-0.68; Table 4).

Discussion

Currently, there are limited therapeutic options for patients with HER2+ breast cancer who develop progressive CNS disease after cranial radiotherapy. In this prospective, multicenter study, 6% of patients experienced a CNS objective response with single-agent lapatinib according to stringent composite criteria, including central radiology review. In exploratory analyses, 21% of patients experienced at least a 20% reduction in CNS tumor volume. Although these patients did not meet criteria for an objective response, an association was observed between 20% volumetric reductions of brain lesions with lapatinib and both PFS and improvement of tumor-related NSS. Thus, although the threshold for CNS activity based on the statistical hypothesis was not met, lapatinib was found to provide modest yet clear evidence of antitumor activity in patients with recurrent brain metastases.

To our knowledge, this is the largest, prospective trial conducted to date for patients with HER2+ breast cancer and progressive CNS disease after cranial radiotherapy. That more than 240 patients were enrolled into this study within a 12-month interval speaks to the magnitude of the problem. As the survival of patients with HER2+ breast cancer, even after a CNS diagnosis, continues to improve, the need for effective salvage therapies after cranial radiotherapy will only increase (14). In addition, the development of effective therapies for refractory brain metastases may ultimately lead to strategies to prevent the emergence of brain metastases.

The antitumor activity of lapatinib in the CNS observed in the previous, smaller, phase 2 study, and confirmed in the present study, seems comparable to that observed outside of the CNS. As first-line treatment for patients with advanced HER2-overexpressing breast cancer, lapatinib resulted in a 4% objective response rate (15). Lapatinib's activity is more modest in patients with progressive extra-CNS disease after trastuzumab, with an objective response rate of 4.3% by investigator assessment and 1.4% by independent assessment (16).

These observations raise questions about the nature of the CNS sanctuary in patients with HER2+ breast cancer. If tumor seeding to the CNS occurs early in the course of disease (i.e., before the emergence of trastuzumab resistance), then one might have expected a CNS response rate similar to that of patients treated with lapatinib in the first-line setting. That the response rate in the current study was comparable to that in studies of refractory patients with extra-CNS disease suggests several possibilities. First, drug delivery to the CNS might be different from non-CNS sites. Alternatively, CNS seeding might be a continuous process, in which case, CNS metastases would be expected to show similar resistance to HER2-directed therapy as extra-CNS metastases. It is conceivable that the rate of CNS response would have been higher in patients not previously exposed to trastuzumab; this study was not designed to address this question. Unfortunately, paired CNS and extra-CNS tissue

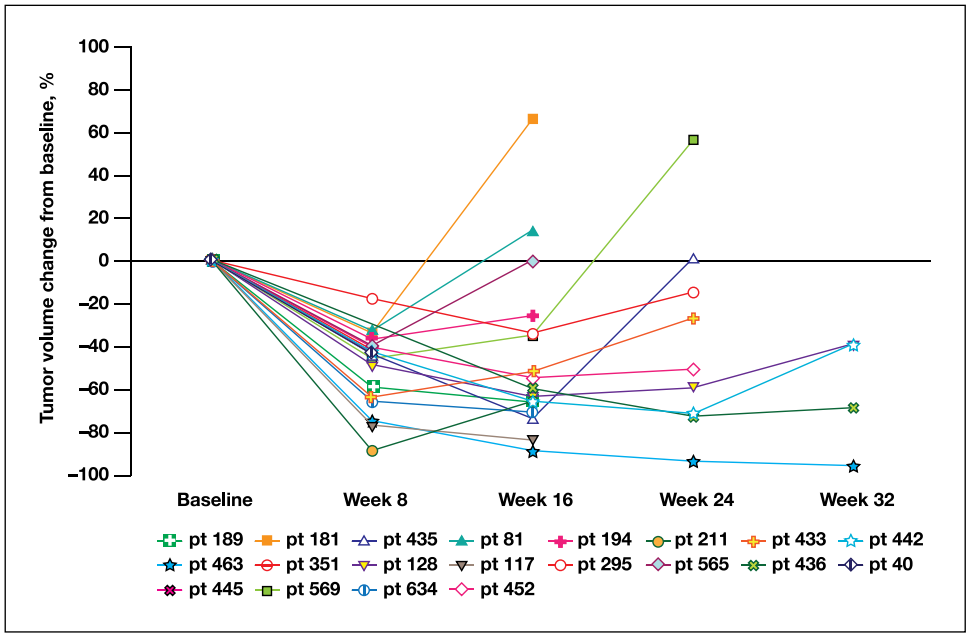

Fig. 2. Duration of CNS tumor regression for patients on lapatinib plus capecitabine extension with ≥20% CNS tumor volume reduction.

was not available for molecular characterization, but if such a resource were available, it could open a valuable window into the metastatic process.

Our study had some limitations. We did not directly assess intratumoral levels of lapatinib and therefore cannot rule out the possibility of suboptimal penetration across the blood-tumor barrier. Despite this limitation, we observed unequivocal evidence of tumor regressions, with a response rate comparable to that of large phase 2 studies for trastuzumab-refractory extra-CNS disease. It is unknown if prior radiotherapy, which was required in all patients, influenced the response to lapatinib by altering the tumor or its microenvironment, including the blood-tumor barrier. However, we did not observe significant differences in the rate of objective response according to the time from the most recent cranial radiotherapy. Next, no comparator arm was used, as there are no approved systemic therapies for refractory brain metastases. There have been few prospective trials of systemic therapy for refractory CNS metastases in the modern era, and existing studies have not been limited to patients with HER2+ disease, which limits the ability to make meaningful cross-trial comparisons. Furthermore, a phase III study of lapatinib versus observation in this setting will likely never be mounted, and therefore, we cannot rule out the possibility that the stabilizations observed could have occurred even without active treatment. However, given that all patients were required to have radiographically documented evidence of CNS progression at the time of study entry, we feel this is relatively unlikely. We also did not include a patient-rated quality-of-life instrument in this study and therefore cannot draw any conclusions about the effect of lapatinib on global quality-of-life. However, we did note an association between improvement of NSS and volumetric reduction of CNS lesions, suggesting that the CNS responses observed in the study were associated with clinical benefit. Further studies could explore the relationship between NSS and quality-of-life. Finally, the clinical significance of 20% reductions in CNS tumor volume is not well-established. However, in both the current study and in a previous, smaller study of lapatinib for brain metastases, we found that patients who achieved some degree of volumetric reduction experienced longer PFS, supporting the hypothesis that such changes are clinically relevant (11). This hypothesis could be further tested in future studies.

With respect to the extension phase of the study, clinically significant and durable CNS objective responses were observed in 20% of patients treated with lapatinib plus capecitabine after disease progression on single-agent lapatinib. Overall, 40% of patients achieved a 20% or greater reduction in the volume of CNS lesions. Because of the study design, we cannot exclude the effect of capecitabine alone. Several case reports have described CNS activity with capecitabine, and CNS responses were observed in a phase I study of capecitabine plus temozolomide (17, 18). However, in the context of the totality of data across lapatinib studies, it is equally plausible that lapatinib adds to the activity of capecitabine both outside of and within the CNS. Despite its modest single-agent activity, lapatinib augments the response rate and increases time to progression in patients with refractory HER2+ breast cancer compared with capecitabine alone (12). Anecdotally, objective responses in the CNS have also been reported with lapatinib plus capecitabine in patients enrolled in the lapatinib expanded access program who received prior capecitabine for systemic disease (19).

In summary, lapatinib is associated with regressions of CNS metastases in patients who have progressed despite trastuzumab and radiotherapy. Additional activity was seen when capecitabine was added to lapatinib. On the basis of the results of this study, prospective studies of lapatinib in combination with other chemotherapeutic agents, novel targeted agents, and cranial radiotherapy are ongoing.

Disclosure of Potential Conflicts of Interest

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In addition to the authors of this article, the participating investigators included Frances Boyle (Mater Hospital, North Sydney, Australia), Nicole McCarthy (Royal Brisbane and Women's Hospital, Herston, Australia), Damien Weber (Hopital Cantonal Universitaire de Geneve, Geneva, Switzerland), Wolfgang Eiermann (Rotkreuzkrankenhaus, Munich, Germany), Franco Nolè (Istituto Europeo di Oncologia di Milano, Milan, Italy), Henrik Lindman (Akademiska Sjukhuset, Uppsala, Sweden), Sankha Suvra Mitra (Royal Sussex County Hospital, Brighton, United Kingdom), Yee Tham (Baylor College of Medicine, Houston, TX), Michael Naughton (Washington University Medical School, St. Louis, MO), David Loesch, (Central Indiana Cancer Centers, Indianapolis, IN), Douglas Yee (University of Minnesota, Division of Hematology/Oncology, Minneapolis, MN), Angela DeMichele (University of Pennsylvania, Philadelphia, PA), Arlene Chan (Mount Medical Centre, Perth, Australia), Catherine Shannon (Mater Adult Hospital, South Brisbane, Australia), Tamara Shenkier (BC Cancer Agency, Vancouver Centre, Vancouver, Canada), Natasha Leighl (Princess Margaret Hospital, Toronto, Canada), Marc Espie (Hôpital Saint Louis, Paris, France), Michelle Melisko (University College of San Francisco, San Francisco, CA), Anna Storniolo (Indiana University, Indianapolis, IN), Charles Vogel (Neurology Clinical Research, Plantation, FL), Lisa Carey (University of North Carolina, Chapel Hill, NC), Ernst Kubista (AKH Wien, Vienna, Austria), Sudarshan Selva-Nayagam (Royal Adelaide Hospital, Adelaide, Australia), Jose Baselga (Hospital Universitario Valle de Hebron, Barcelona, Spain), Pierre Fumoleau (CRLCC Georges-Franc̆ois Leclerc, Dijon Cedex, France), Radheshyam Naik (Rajalakshmi Polyclinic and Nursing Home, Bangalore, India), Hiroji Iwata (Aichi Cancer Center Hospital, Aichi, Japan), Tadeusz Pienkowski (Instytut im. Marii Sklodowskiej Curie, Warsaw, Poland), Agnieszka Jagiello-Gruszfeld (Samodzielny Publiczny Zespol Pulmonologii i Onk., Olsztyn, Poland), Ching-Hung Lin (National Taiwan University Hospital, Taipei, Taiwan), Tsu-Yi Chao (Tri Service General Hospital, Taipei, Taiwan), Monica Fornier (Memorial Sloan-Kettering Cancer Center, New York, NY), Donald A. Richards (Tyler Cancer Center, Tyler, TX), Jacquie Chirgwin (Box Hill Hospital, Box Hill, Australia), Rashida Haq (Saint Michael's Hospital, Toronto, Canada), Augusto Pedrazzini (Humaine Clinica Santa Chiara, Locarno, Switzerland), Shigehira Saji (Tokyo Metropolitan Komagome Hospital, Tokyo, Japan), Yasuhiro Fujiwara (National Cancer Center Hospital, Tokyo, Japan), Yoshinori Ito (The Cancer Institute Hospital of JFCR-Ariake, Tokyo, Japan), Masaru Narabayashi (Saitama Medical School Hospital, Saitama, Japan), Chao-Jung Tsao (Chi-Mei Hospital, Tainan, Taiwan), Daniel Hayes (University of Michigan, Ann Arbor, MI), Hannah Linden (University of Washington, Seattle, WA), Melanie Royce (University of New Mexico Health Sciences Center, Albuquerque, NM), Stephen Kahanic (Sioux Land Cancer Institute, Sioux City, IA), and Malcolm H. Purdy (Hematology Oncology Associates, Albuquerque, NM).

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