

Translational Breast Cancer Research Consortium (TBCRC) 022: A Phase II Trial of Neratinib for Patients With Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases

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ABSTRACT

Purpose

Evidence-based treatments for metastatic, human epidermal growth factor receptor 2 (HER2)–positive breast cancer in the CNS are limited. Neratinib is an irreversible inhibitor of erbB1, HER2, and erbB4, with promising activity in HER2-positive breast cancer; however, its activity in the CNS is unknown. We evaluated the efficacy of treatment with neratinib in patients with HER2-positive breast cancer brain metastases in a multicenter, phase II open-label trial.

Patients and Methods

Eligible patients were those with HER2-positive brain metastases (≥ 1 cm in longest dimension) who experienced progression in the CNS after one or more line of CNS-directed therapy, such as whole-brain radiotherapy, stereotactic radiosurgery, and/or surgical resection. Patients received neratinib 240 mg orally once per day, and tumors were assessed every two cycles. The primary endpoint was composite CNS objective response rate (ORR), requiring all of the following: $\geq 50\%$ reduction in volumetric sum of target CNS lesions and no progression of non-target lesions, new lesions, escalating corticosteroids, progressive neurologic signs/symptoms, or non-CNS progression—the threshold for success was five of 40 responders.

Results

Forty patients were enrolled between February 2012 and June 2013; 78% of patients had previous whole-brain radiotherapy. Three women achieved a partial response (CNS objective response rate, 8%; 95% CI, 2% to 22%). The median number of cycles received was two (range, one to seven cycles), with a median progression-free survival of 1.9 months. Five women received six or more cycles. The most common grade ≥ 3 event was diarrhea (occurring in 21% of patients taking prespecified loperamide prophylaxis and 28% of those without prophylaxis). Patients in the study experienced a decreased quality of life over time.

Conclusion

Although neratinib had low activity and did not meet our threshold for success, 12.5% of patients received six or more cycles. Studies combining neratinib with chemotherapy in patients with CNS disease are ongoing.

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INTRODUCTION

Patients with metastatic, human epidermal growth factor receptor 2 (HER2)–positive breast cancers often face significant challenges once their disease progresses through standard trastuzumab-based regimens, and approximately one half of

patients will ultimately develop parenchymal brain metastases.¹⁻⁷ Upfront therapy for newly diagnosed brain metastases typically includes whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), or both, and a small proportion of patients undergo surgical resection for limited disease. Historically, survival after diagnosis of CNS disease was poor, and many patients

died of progressive disease⁸; however, recent studies have suggested that median survival for patients with CNS disease may be improving, particularly for those with HER2-positive disease, likely as a result of advances in systemic therapy.⁹⁻¹³ Unfortunately, standard therapies after CNS progression remain undefined. Few prospective clinical trials have been conducted in the modern era, and many trials evaluating novel agents specifically exclude patients with active CNS disease.

Neratinib is a potent, oral, irreversible-binding inhibitor of the erbB family of receptor tyrosine kinases that inhibits signal transduction through erbB1, HER2, and erbB4.¹⁴⁻¹⁷ Although CNS penetration by neratinib is not well described, preclinical models suggest limited penetration,¹⁸ with concentrations similar to those observed in the brains of healthy animals who received lapatinib,¹⁹ an agent known to produce responses in the brain.^{20,21} Thus, low CNS concentrations do not necessarily preclude potential CNS activity, particularly in the setting of a disrupted blood-tumor barrier. Given the promising activity for neratinib monotherapy¹⁶ and the potential for CNS penetration as a small molecule, we conducted a two-stage, phase II, single-arm study to evaluate the efficacy of treatment with neratinib in women with HER2-positive brain metastases.

PATIENTS AND METHODS

Study Cohort

Adult patients with HER2-positive,²² invasive breast cancer and measurable CNS disease (one or more parenchymal brain lesions measuring ≥ 10 mm in the longest dimension) whose cancers progressed in the CNS after any previous CNS-directed therapy (WBRT, SRS, surgery, or any combination) were eligible. Other key inclusion criteria included Eastern Cooperative Oncology Group performance status of 0 to 2 and a cardiac ejection fraction of $\geq 50\%$. There was no limit on the number of previous therapy lines; previous lapatinib, but not previous neratinib, was allowed. Patients were excluded if they had escalating corticosteroids during the week before baseline imaging, more than two seizures over the 4 weeks before study entry, significant malabsorption syndrome, inability to tolerate oral medications, or any pre-existing, chronic, grade ≥ 2 diarrhea.

The study was conducted through the Translational Breast Cancer Research Consortium, and all women signed an informed consent approved by the institutional review boards of each participating institution. Participating centers included the Dana-Farber/Harvard Cancer Center (Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, and Massachusetts General Hospital), Baylor College of Medicine and its affiliate Ben Taub Hospital, Johns Hopkins University, University of California, San Francisco, University of Michigan, Duke University, and the University of Pittsburgh.

Treatment Plan

This was a two-stage, phase II, open-label, single-arm study. Oral neratinib 240 mg was administered once per day without breaks, and cycle duration was 28 days. All patients were evaluated with a neurologic exam on the first day of each cycle. Evaluations included neurologic symptoms (ie, headache, dizziness, etc), cranial nerve and motor strength assessments, presence of aphasia and dysphasia, ataxia, somnolence sensation, and global assessment of worsening, stability, or improvement. Patients were reimaged every two cycles with magnetic resonance imaging of the brain and computed tomography scans of the chest-abdomen-pelvis.

Patients were to remain on study treatment until tumor progression, unacceptable toxicity and/or adverse event, severe intercurrent illness,

request to come off study, study closure, or any changes in the condition of the participant that rendered the participant unacceptable for further treatment. Treatment holds and/or dose reductions were required for patients who experienced prolonged grade ≥ 2 diarrhea, grade ≥ 2 pneumonitis, grade ≥ 3 nausea and vomiting or rash, or any grade 4 toxicity. An amendment mandating loperamide 2 mg once per day during cycle 1 was approved on May 14, 2012, at the Dana-Farber Cancer Institute (and subsequently approved at all sites). In total, 28 of 40 patients received prophylactic loperamide.

In an optional extension cohort, patients who experienced non-CNS progression by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1^{23,24} but who had stable disease (SD), a partial response (PR), or a complete response (CR) in the CNS had the option to continue therapy with neratinib (at the current dose) along with standard dose trastuzumab (administration weekly or every three weeks).

Two additional cohorts are still enrolling patients in this protocol, including a cohort of patients deemed eligible for surgical resection (cohort 2) and a cohort of women with progressive CNS disease who receive concurrent neratinib and capecitabine (cohort 3). Results of cohort 1 are presented here.

Correlative Studies

Correlative studies for women in our study included a research blood draw at baseline to be processed using the CellSearch Circulating Tumor Cells (CTC) method (Janssen Diagnostics, Raritan, NJ).^{25,26} We also examined longitudinal neurocognitive function and quality of life (QOL) for women at baseline compared with end of treatment. If progression occurred before cycle 2 or 3 testing, the most recent testing served as end of treatment. Neurocognitive testing included the Hopkins Verbal Learning Test-Revised (HVLT-R; learning and memory), the Trail Making Test Parts A (for processing speed) and B (for executive function), and Controlled Oral Word Association (for executive function). To assess QOL, patients completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30)/BN20.²⁷⁻²⁹

Statistical Analyses

The primary end point assessed was objective response rate (ORR; to include CR and PR) in the CNS, according to composite criteria.²¹ Measurement of CNS lesions was performed centrally by the Harvard Tumor Imaging Metrics Core. Non-CNS evaluation was completed by local investigators, per RECIST 1.1.^{23,24} An objective CNS PR was defined as $\geq 50\%$ reduction in the sum volume of CNS target lesions, without new lesions, systemic disease progression, clearly worsening neurologic status (either by neurologic examination or by neurologic symptoms), or increase in corticosteroid dose. A CR was defined as disappearance of all target lesions in addition to the PR criteria. Progressive disease (PD) was defined as $\geq 40\%$ increase in the sum of target lesions, any new lesion ≥ 6 mm, systemic progression, clearly worsening neurologic status, or significant increase in corticosteroid dose. If a tumor progressed in a non-CNS site first or a patient died or withdrew from the study for any reason after receiving at least one dose of the drug and before a response was determined, she was considered a nonresponder. In the few cases ($n = 3$) for which CNS progression was suspected locally but not confirmed centrally, patients were allowed to continue on the study until the next imaging assessment. If progression was then noted, the time of progression was documented as the first suspected progression.

Secondary objectives assessed included time to progression, overall survival (OS), response by bidirectional CNS response criteria (PR, $\geq 50\%$ decrease; PD, $\geq 25\%$ increase in the sum of the longest diameters),³⁰ response according to Response Assessment in Neuro-Oncology Brain Metastases Working Group criteria³¹ (PR, $\geq 30\%$ decrease in the sum of the longest diameters of CNS disease for ≥ 4 weeks with no new lesions, stable and/or improved clinical condition, and stable and/or decreased corticosteroid dose), safety and tolerability, and associations of baseline

CTC count and OS. In exploratory analyses, we examined changes in neurocognitive function and QOL at end of treatment versus baseline.

The study had a two-stage design on the basis of a binomial distribution with constant probability of response, with an accrual goal of 40 patients. In the first stage, if one or more patients of 18 had a response, another 22 patients would be enrolled. All patients who received one dose of the study drug were included in analyses. If five or more patients of 40 achieved a CNS response, the drug would be deemed worthy of future study as a single agent. This two-stage design had 92% power to detect a true response of $\geq 20\%$ (alternative hypothesis) against the true response rate of 6% (null hypothesis) while maintaining a one-sided type I error rate of 9%.

CTC Analysis

We examined associations of CTC count at baseline and OS for women in the study. We tested whether the percent of patients living more than 6 months after study entry in the group with less than five CTC per 7.5 mL of whole blood was significantly greater than the percent of patients living more than 6 months in the group with five or more CTC per 7.5 mL (one-sided Fisher's exact test) on the basis of a previous work demonstrating the importance of this threshold.³²

Neurocognitive Function and QOL

We compared baseline values to end-of-treatment values for HVL-T-R Total Recall, HVL-T-R Delayed Recall, HVL-T-R Delayed Recognition, Trail Making Test Parts A and B, and Controlled Oral Word Association in two ways: by using standardized scores adjusted for age and education,³³⁻³⁵ and using the Reliable Change Index.³⁶ The standardized scores were compared using the Wilcoxon signed rank test for paired data.

To assess QOL, we focused on seven EORTC QLQ-C30 QOL measures: global health status, physical functioning, cognitive functioning, diarrhea, fatigue, nausea and vomiting, and emotional functioning. These measures were constructed from the individual item values using the formulae in the EORTC QLQ-C30 version 3.0 manual. We compared baseline values to end-of-treatment values by using the Wilcoxon signed rank test for paired data.

RESULTS

Patient Characteristics

A total of 40 women enrolled in the study between February 2012 and June 2013 at seven Translational Breast Cancer Research Consortium centers. Baseline characteristics are shown in Table 1.

Efficacy

As of January 1, 2015, no patients remained on the study treatment; 34 patients had died, two were lost to follow-up, and four remained alive. The median number of cycles received before any extension therapy was two (range, one to seven cycles). Five women received six or more cycles of therapy. One patient experienced a PR in the first stage of the study ($n = 18$), and the second stage enrolled to completion ($n = 22$). Three patients had an ORR (8%; 95% CI, 2% to 22%) and no patients experienced a CR (Fig 1; Table 2). In the three responders, duration of response was six cycles in one patient and four cycles in two patients; all three responders had received previous treatment with lapatinib. Of those without previous WBRT ($n = 9$), one patient experienced a PR, four had SD, and three had PD as the best CNS response; one patient was not evaluable. Of the six women who had not received previous treatment with lapatinib, five came off

Table 1. Patient Characteristics for the Cohort

Characteristic	Value
Median age, years (range)	51 (35-65)
Female	40 (100)
ECOG PS	
0	15 (38)
1	13 (33)
2	12 (30)
Race	
White	34 (85)
Black/other	6 (15)
Non-CNS sites of disease	
Lung	15 (38)
Liver	16 (40)
Bone	26 (65)
Chest wall	2 (5)
ER-positive disease	18 (45)
Previous CNS therapy*	
WBRT alone	15 (38)
SRS alone	9 (23)
WBRT and SRS	16 (40)
Previous surgical resection of CNS disease	12 (30)
Previous systemic therapy for metastatic disease	
No previous chemotherapy	2 (5)
≥ 2 previous lines	33 (83)
Trastuzumab	36 (90)
Lapatinib	34 (85)

NOTE. N = 40. All data are given as No. (%) unless otherwise specified. Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PS, performance status; SRS, stereotactic brain surgery; WBRT, whole brain radiotherapy.

*Patients may have received more than one previous CNS therapy. Totals do not sum to 100.

treatment as a result of progression by four cycles (range, one to four cycles) and one came off treatment as a result of toxicity during cycle 1.

Reasons for discontinuation of study treatment included radiographic CNS progression ($n = 23$), clinical CNS progression ($n = 6$), non-CNS progression ($n = 2$), both CNS and non-CNS progression ($n = 3$), and toxicity ($n = 6$). Two patients who experienced non-CNS progression received trastuzumab-neratinib on the extension cohort after one and two cycles of neratinib, respectively. One of these patients received two extension cycles and the other received 15; neither experienced a CNS response during extension therapy.

Regarding secondary clinical outcomes, four women (10%) experienced a CNS response by bidirectional criteria. Seven patients had discordant results for their best volumetric and bidirectional response (five patients had PD by volume but SD by bidirectional criteria; one patient had SD by volume but PR by bidirectional criteria; and one patient had SD by volume but PD by bidirectional criteria). All three partial responders by volume also had responses by bidirectional criteria. For responses by Response Assessment in Neuro-Oncology Brain Metastases Working Group criteria,³¹ two (5%) women had confirmed PRs and two (5%) had unconfirmed PRs (response of ≥ 4 weeks could not be confirmed).

The median time to progression for women in the study was 1.9 months (all progressed, no censoring), and the median OS was 8.7 months, with 30% of women still alive at 12 months after study registration (Figs 2A and 2B).

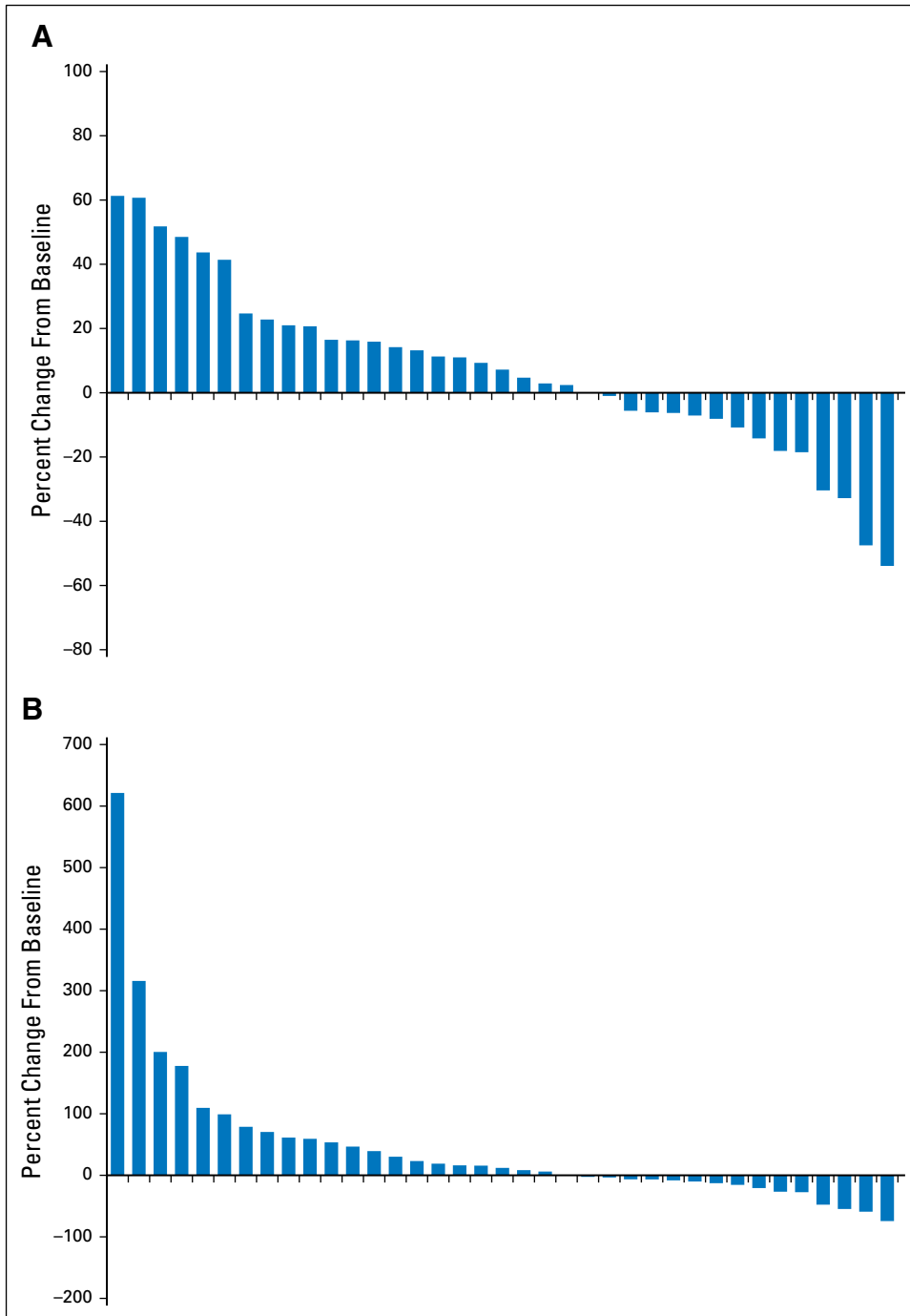


Fig 1. Waterfall plot for best (A) volumetric response and (B) bidirectional response in each patient who had baseline imaging and at least one staging exam (n = 37).

Toxicity

Adverse events for women in the study are shown in [Table 3](#). The most common grade 3 event was diarrhea (23%), but the event rate decreased for patients who received prophylactic loperamide. Of 28 patients who received prophylaxis, 11% had grade 2 diarrhea and 21% had grade 3 diarrhea. Of those who did not receive prophylaxis (n = 12), 25% had grade 2 diarrhea, 25% had grade 3 diarrhea, and 4% (n = 1) had grade 4 diarrhea. Six patients required dose reductions (for diarrhea in three patients, for nausea and diarrhea in two patients, and for liver function in one patient).

No additional grade ≥ 2 toxicities were reported for the two patients who received extension therapy with trastuzumab.

CTCs

Thirty-one patients had usable CTC samples drawn at baseline and were included in this analysis, nine of whom had a CTC of five or more. Baseline CTCs ranged from zero to 379 (median of 0; zero CTC [55%]; one to 10 [26%]; 11 to 20 [3%]; 21 to 50 [10%]; and > 50 [6%]). Of patients with a CTC five or more,

Table 2. Best CNS Response According to Composite Criteria

Best Response	Cohort 1 (N = 40)
CR	0 (0)
PR	3* (8; 95% CI, 2% to 22%)
SD six or more cycles	4 (10)
SD less than six cycles	12 (30)
PD	
PD in CNS only	10 (25)
Symptomatic deterioration/clinical progression (CNS or non-CNS)	7 (18)
PD in CNS and non-CNS	2 (5)
Off treatment before restaging for toxicity	2 (5)

NOTE. Composite CNS objective response rate required all of the following: $\geq 50\%$ reduction in volumetric sum of target CNS lesions, no progression of nontarget lesions, no new lesions, no escalating steroids, no progressive neurologic signs and symptoms, and no non-CNS progression. Data are given as No. (%) unless otherwise specified.

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

*One responder received treatment for six cycles and was not included in the SD for six or more cycles category; two responders received four cycles of study treatment.

Table 3. Grade ≥ 2 Adverse Events (No., %) for Women in the Study

Toxicity	Grade 2	Grade 3	Grade 4
Diarrhea*†	6 (15)	9 (23)	1 (3)
Nausea and vomiting	3 (8)	2 (5)	
Constipation	2 (5)		
Anorexia	3 (8)		
Dehydration†		1 (3)	
Dyspepsia	2 (5)		
Mucositis	1 (3)	1 (3)	
Fatigue	6 (15)		
Decreased LVEF	1 (3)		
Hypotension†		1 (3)	
Sinus tachycardia†		1 (3)	
Peripheral sensory neuropathy	1 (3)		
Liver function tests	1 (3)	1 (3)	
Headache	1 (3)		

NOTE. N = 40. Toxicities are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Each grade is counted once as the worst grade experienced by the patient for each event. Included toxicities are those deemed by the investigator to be possibly, probably, or definitely related to treatment.

Abbreviation: LVEF, left ventricular ejection fraction.

*Of 28 patients who received prophylaxis, three had grade 2 diarrhea (11%) and six had grade 3 diarrhea (21%). Among the 12 patients who did not receive prophylaxis, three had grade 2 diarrhea (25%), three had grade 3 diarrhea (25%), and one had grade 4 diarrhea (4%).

†All three events occurred in the same patient and were associated with grade 3 diarrhea.

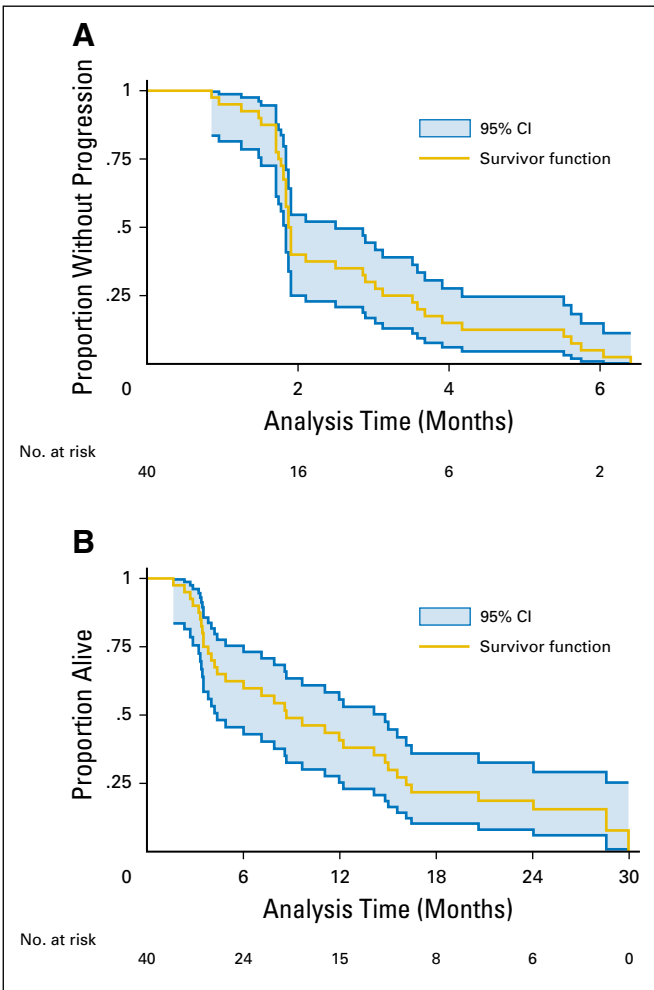


Fig 2. (A) Time to progression and (B) overall survival for women treated with neratinib (n = 40).

five (56%) lived longer than 6 months (95% CI, 21% to 86%) compared with 13 of those with a CTC less than five (59%; 95% CI, 36% to 79%; Fisher's exact $P = 1.00$).

Neurocognitive Function and QOL

Results for patients who completed baseline neurocognitive testing are shown in Appendix Table A1 (online only). Median test performance was generally in the average range at baseline, though large variability was observed. Median difference scores over time declined with a measure of memory (HVLT-R Delayed Recall) on five of six tests, reaching significance ($P < .05$) on the basis of the Wilcoxon signed rank (Table 4). According to the Reliable Change Index criteria, the majority of patients remained stable whereas a subgroup (0% to 36% on one or more tests) exhibited objective decline, with the most frequently observed decline occurring on a measure of learning and memory (HVLT-R). Global QOL, fatigue, and diarrhea all worsened with time (Appendix Table A2, online only).

DISCUSSION

In this phase II, single-arm study, we evaluated the efficacy and toxicity of single-agent neratinib in patients with progressive, HER2-positive brain metastases. The CNS ORR for neratinib monotherapy was low and did not meet its prespecified threshold for success among a highly treatment-refractory population, though clinical activity was observed and five patients (12.5%) remained on treatment for at least six cycles. Although diarrhea was initially common, rates substantially

Table 4. Results for Changes in Neurocognitive Function From Baseline to Off Treatment for Women With Paired Results Available

Test	No. of Patients With Data Available	Median Difference	Wilcoxon SRT <i>P</i>	Improved (%)*	Stable (%)*	Worsened (%)*
HVLT-R Total Recall	22	-0.13	.40	9	51	32
HVLT-R Delayed Recall	22	-0.59	.04	5	59	36
HVLT-R Delayed Recognition	22	0.00	.57	14	55	32
Trail Making Test Part A	22	-0.38	.26	18	64	18
Trail Making Test Part B	17	-0.49	.21	18	58	24
COWA	22	-0.15	.99	14	86	0

Abbreviations: COWA, Controlled Oral Word Association; HVLT-R, Hopkins Learning Verbal Test-Revised; SRT, signed rank test.

*Data obtained by using the Reliable Change Index from baseline to off treatment.

decreased with prophylactic loperamide. To lower diarrhea events further, loperamide prophylaxis has since been instituted in all neratinib protocols at higher doses than were used in our study (total, 16 mg/d).

Neratinib monotherapy has demonstrated promising clinical activity in HER2-positive extracranial disease in past trials,¹⁶ but it resulted only in a low CNS ORR in our study, similar to that seen with lapatinib monotherapy.^{21,37} Despite the low number of CNS responses observed with lapatinib and neratinib when used as monotherapy, studies of CNS tissue penetration of lapatinib in patients with glioblastoma multiforme and breast cancer CNS metastases have demonstrated significant concentrations of lapatinib in CNS surgical specimens, perhaps because of a disrupted blood-brain barrier or an inhibition of efflux transporters.^{19,38,39} Cohort 2 of our protocol is still enrolling and will provide important data on neratinib penetration in CNS tumors and CSF; patients in this cohort will receive neratinib pre- and postoperatively, and will have drug concentrations assessed in brain parenchyma, CSF, and plasma.

It is possible that even though lapatinib, and possibly neratinib, crosses the blood-tumor barrier, activity may be optimized when administered in combination with other agents. This may at least partially explain the higher CNS response rates observed when lapatinib is combined with capecitabine.^{20,21,40} A phase I and II protocol of neratinib-capecitabine in the setting of metastatic HER2-positive breast cancer demonstrated robust systemic activity⁴¹ and has provided the rationale for the NALA study (A Study of Neratinib Plus Capecitabine *v* Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2 Directed Regimens in the Metastatic Setting, ClinicalTrials.gov NCT01808573), which randomly assigns patients with metastatic HER2-positive disease to receive capecitabine-neratinib versus capecitabine-lapatinib. Although women with active brain metastases are not eligible for NALA, we are currently enrolling patients in a third cohort of our study, which is evaluating capecitabine-neratinib in patients with progressive CNS disease. We hypothesize that the combination may be more effective than single-agent neratinib, although this remains to be seen.

Although CTC count has been associated with survival in patients with metastatic breast cancer and in those with CNS metastases,^{32,42,43} our results were not conclusive. The lack of consistency in these findings may be related to differences in patient populations, varying disease burden, disease sites, and disease subtypes, and suggests the possibility that a CTC of five may not be a relevant threshold for all patient groups.

Our findings for worsened neurocognitive function test results for patients at end of treatment were not surprising given that most patients had experienced progression and most patients had received WBRT, a treatment known to impact learning and memory. Although direct comparisons with other brain metastasis populations are fraught with difficulty, the current study population exhibited better neurocognitive function than did those in most published samples.⁴⁴⁻⁴⁶ Given that neurocognitive function is a good prognostic factor for survival time, it is also not surprising that many patients remained alive longer than expected. Furthermore, our QOL results showed expected changes in worse global health status, increased fatigue, and increased diarrhea over time.

We recognize several study limitations. First, this was a small, phase II study without a comparison arm, and patients had a diverse set of past CNS-directed treatments. Our study population was heavily pretreated with a high burden of systemic disease, and several patients also had longstanding CNS disease. Second, because of the low number of responders, an examination of predictors of response is not possible. In addition, although it is possible that previous treatments, such as lapatinib, may limit responses, all of the responders in our study received previous lapatinib. Although these clinical issues may have led to an underestimation of the CNS activity of neratinib, our results did not meet the threshold to prompt continued investigation of neratinib monotherapy in this clinical context. In a currently enrolling cohort (cohort 3), neratinib and capecitabine are being administered in combination, and separate cohorts will enroll patients who have either not received (cohort 3a) or received (cohort 3b) previous lapatinib.

Beyond these specific trial results, the rapid accrual of this trial and others focused on brain metastases highlights the unmet medical need for new therapies for brain metastases as well as the feasibility of conducting trials in this patient population. Further study of potentially active CNS agents is crucial to improve QOL and duration of life for patients with progressive metastatic breast cancer of the brain. Results from ongoing treatment cohorts will be forthcoming.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix**Table A1.** Summary of Baseline Data for Neurocognitive Function Analyses for Patients With Baseline Data

Test	No. of Patients With Data Available	Median (Range)
HVLT-R Total Recall	37	-1.5 (-6.3-1.1)
HVLT-R Delayed Recall	36	-1.4 (-6.1-1.2)
HVLT-R Delayed Recognition	36	-0.2 (-11.1-0.9)
Trail Making Test Part A	35	0.1 (-31.6-1.4)
Trail Making Test Part B	33	-1.1 (-169-1.4)
COWA	33	-0.7 (-3.4-0.8)

NOTE. HVLT-R assessed learning and memory; Trail Making Test Parts A and B assessed processing speed and executive function; and COWA assessed executive function.

Abbreviations: COWA, Controlled Oral Word Association; HVLT-R, Hopkins Verbal Learning Test-Revised.

Table A2. Quality of Life From Baseline to End of Treatment

Test	No. of Patients With Paired Data Available*	Median Difference	Wilcoxon SRT <i>P</i>
Global health status†	22	-12.5	.029
Physical functioning	24	0.0	.37
Cognitive functioning	23	0.0	.31
Diarrhea‡	23	0.0	.017‡
Fatigue§	22	11.1	.0016
Nausea and vomiting	23	0.0	.46
Emotional functioning	22	0.0	.61

NOTE. Paired data available for 22 to 24 patients using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30/BN20. Abbreviation: SRT, signed rank test.

*For seven patients, C2 data were used for end-of-treatment data.

†For global health status, larger values are better; a negative difference indicates that a patient got worse. The differences were somewhat larger in patients whose end of treatment was beyond two cycles (median, -16.7) compared with patients with only one or two cycles (median, -12.5), but this difference was not statistically significant ($P = .44$).

‡Although the median difference for diarrhea is 0.0, of the 23 patients with data, 10 patients got worse, whereas two got better and 11 stayed the same.

§For fatigue, larger values are worse; a positive difference indicates that a patient got worse.