Title

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Abstract

Background: Improving outcomes for patients with human epidermal growth factor 2-positive (HER2+) central nervous system (CNS) metastases remains an unmet clinical need. This trial evaluated a novel combination of everolimus, lapatinib and capecitabine for this disease.

Methods: Patients with trastuzumab-pretreated, HER2+ breast cancer brain metastasis without prior therapy with a mammalian target of rapamycin (mTOR) inhibitor were eligible. Patients received lapatinib and everolimus daily (continuously) and capecitabine twice daily (d1–14) in 21-d cycles. The primary endpoint was the 12-week CNS objective response rate (ORR). Secondary endpoints included safety, progression-free survival (PFS), overall survival (OS), best CNS ORR and extra-CNS ORR.

Results: A total of 19 participants were enrolled and treated with ⩾1 dose of the study drug. The median age was 58.5 years, the median number of therapies for metastatic breast cancer was 2.5 (0–11). Pretrial, 74% of participants had received prior lapatinib, capecitabine or both. A total of 63% had received previous CNS radiation or surgical resection and CNS radiation. The maximum tolerated doses were lapatinib at 1000 mg, everolimus at 10 mg, and capecitabine at 1000 mg/m^2. Phase II proceeded with capecitabine at 750 mg/m^2 due to better tolerability. The most common grade 3/4 adverse events were mucositis (16%), diarrhea, fatigue, and hypokalemia (11% each). Of 11 participants evaluable for 12-week CNS ORR, 3 (27%) had partial response and 7 (64%) had stable disease. The best CNS ORR in eligible participants was 28% (5/18). The median PFS and OS were 6.2 and 24.2 months, respectively.

Conclusions: This novel triplet combination of lapatinib, everolimus, and capecitabine is well tolerated and yielded a 27% response rate in the CNS at 12 weeks in heavily pretreated participants. Larger studies are warranted to further evaluate this regimen.

Trial registration: ClinicalTrials.gov: NCT01783756. Registered 05 February 2013, https://clinicaltrials.gov/ct2/show/NCT01783756

Keywords: capecitabine, chemotherapy, everolimus, HER2+ breast cancer, lapatinib, metastatic brain tumors, PI3K/Akt/mTOR inhibitor, tyrosine kinase inhibitor

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Introduction

While trastuzumab has dramatically improved outcomes for patients diagnosed with human epidermal growth factor 2-positive (HER2+) breast cancer[1–5] its use has not resulted in a lower incidence rate or substantial responses in central nervous system (CNS) metastases, likely owing to the fact that the blood–brain barrier prevents the entry of large antibodies.[6,7] A phase II trial evaluating the HER1/HER2 inhibitor, lapatinib[8] for patients with progressive breast cancer brain metastases (BCBM) after radiation and trastuzumab demonstrated a 6% objective response rate (ORR) in the CNS and a progression-free survival (PFS) of 2.4 months. In an extension phase of this study, 50 patients whose disease progressed on lapatinib were treated with lapatinib plus capecitabine. Of these, 20% achieved a CNS partial response (PR) and the median PFS was 3.65 months.

Everolimus (RAD001) selectively inhibits the mammalian target of rapamycin (mTOR), a highly conserved kinase that acts as a central regulator of protein synthesis, cell growth, proliferation, angiogenesis and survival through the phosphoinositide 3-kinase (PI3K) signaling pathway.[9–12] Everolimus is United States Food and Drug Administration (US FDA)-approved in combination with exemestane for patients with hormone receptor (HR)-positive HER2-negative advanced breast cancer, previously treated with a nonsteroidal aromatase inhibitor.[13] The mTOR pathway has been implicated as a mechanism of resistance to HER2-targeted therapy. Preclinical data from our laboratory also suggest that everolimus has activity in HER2+ breast cancers.[14] The phase III BOLERO-3 trial demonstrated a modest improvement in PFS when everolimus was added to trastuzumab and vinorelbine in patients with heavily pretreated HER2+ advanced breast cancer.[15] Importantly, murine models indicate significant penetration of everolimus into the CNS.[16]

A phase I clinical trial in patients with advanced cancers evaluated lapatinib plus everolimus and defined 1250 mg of lapatinib and 5 mg of everolimus daily as the maximum tolerated dose (MTD).[17] Additionally, two phase I studies have demonstrated the safety and activity of capecitabine combined with everolimus. The MTDs for capecitabine and everolimus were 1000 mg/m^2 twice daily and 10 mg once daily, respectively in one study[18] and 650 mg/m^2 twice daily and 5 mg twice daily, respectively in the other study.[19]

We initiated an investigator-initiated phase Ib/II multicenter clinical trial to explore the safety and activity of a novel triplet combination of lapatinib, everolimus and capecitabine for patients with progressive HER2+ BCBM.

Methods

Study design and patient eligibility

TRIO-US (Translational Research in Oncology-United States) B-09 is an open-label, multicenter, phase Ib/II single-arm study evaluating the combination of everolimus, lapatinib and capecitabine. Eligible participants included women ⩾18 years with locally-confirmed HER2+ [IHC 3+ or amplified by fluorescence in-situ hybridization (FISH)][20] metastatic breast cancer (MBC) previously treated with trastuzumab. Documented progression of disease (PD) in the brain (⩾1 CNS lesion ⩾10 mm) was required after the most recent therapy. Any number of prior systemic regimens were allowed as long as participant had recovered from grade ⩾2 side effects per National Cancer Institute/National Institutes of Health Common Terminology Criteria for Adverse Events (NIH-NCI CTCAE version 4.03).[21] Prior therapy with lapatinib or capecitabine was allowed. Lapatinib must have been discontinued at least 14 days prior to starting study treatment and previous chemotherapy (including capecitabine) must have been discontinued at least 21 days prior to starting study treatment. Concurrent steroids up to an equivalent of 20 mg prednisone daily, on taper or stable dose for ⩾2 weeks was allowed. Adequate hematologic, renal, and hepatic function were required. Participants were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of ⩽2 with a life expectancy of ⩾12 weeks.[22] Prior treatment with an mTOR inhibitor, leptomeningeal carcinomatosis as the only site of CNS disease, active noncancer-related hepatic or biliary disease, clinically significant interstitial lung disease or history of cardiac disease were exclusionary.

All participants provided written informed consent prior to enrollment. The protocol and informed consent were approved by the Johnson Comprehensive Cancer Center (JCCC) Office of Regulatory Compliance at UCLA (IRB# 12-001358) and by Western-IRB. This is an investigator-sponsored trial by TRIO-US and pharmaceutical sponsors, Novartis and GSK.

Study treatment

All drugs were self-administered orally over 21-day cycles. Everolimus and lapatinib were given once daily continuously and capecitabine twice daily on days 1–14.

An initial 3+3 dose-escalation phase of the study was conducted to evaluate the safety of this combination. Lapatinib was given at a fixed dose of 1000 mg daily. Dose escalation of capecitabine and everolimus were as follows: cohort 1: capecitabine 750 mg/m^2, everolimus 5 mg; cohort 2: capecitabine 750 mg/m^2, everolimus 10 mg; cohort 3: capecitabine 1000 mg/m^2, everolimus 10 mg. Dose reductions for each drug in each cohort were permitted for toxicity. Dose-limiting toxicities (DLTs) were assessed during the first cycle of treatment and defined as NIH-NCI CTCAE version 4.03 grade 3/4 treatment-related toxicity lasting more than 1 week.[21] The dose utilized for the phase II portion of the study was determined from safety information collected during the escalation phase (including safety beyond the cycle 1).

The maximum dose delay allowed for each drug was 21 days. Treatment continued for up to 12 months until PD, unacceptable toxicity or withdrawal of consent. After 12 months, those participants receiving clinical benefit were allowed to continue receiving treatment after sponsor approval.

Study objectives

The primary endpoint was 12-week CNS ORR and included all eligible participants (phase Ib/II) who completed four cycles and underwent brain magnetic resonance imaging (MRI) at 12 weeks. Secondary endpoints were evaluated in all patients who received at least one dose of study medication and included safety, PFS, OS, best CNS ORR, and extra-CNS ORR.

Study assessments

Participants were evaluated by clinical examination and laboratory tests at baseline and every 3 weeks.

CNS response was evaluated per a modified response evaluation criteria in solid tumors (RECIST) version 1.1[23] that allowed the selection of up to five target lesions in the brain. MRI of the brain was performed every 6 weeks through cycle 6, then every 9 weeks. Response was measured by one central radiology reviewer. Clinical neurological assessments using a Neurological Signs and Symptoms (NSS) worksheet were done every time a brain MRI was performed.[8] CNS complete response (CR) required complete disappearance of all enhancing measurable and non-measurable CNS disease sustained at least 4 weeks, no new lesions, stable-to-improved NSS, no progression of extra-CNS disease, and no corticosteroid therapy. CNS PR was defined as 30% decrease in the sum of diameters of target lesions for at least 4 weeks (with confirmatory MRI administered at 4 weeks), no new lesions, stable-to-improved NSS, no progression of extra-CNS disease, with the patient on a stable or lower dose of corticosteroid therapy compared with baseline. PD included any of the following: new CNS lesions, progression of CNS lesions, tumor-related increase in steroid dose compared with baseline or best response, new or worsening tumor-related NSS, or progression of extra-CNS disease. Stable disease required there to be no CR, PR nor PD and stable or lower dose of steroids compared with baseline with stable-to-improved NSS.

Radiographic assessment of extra-CNS response with MRI or computed tomography (CT) scans (or proton emission tomography/CT) of the chest and abdomen was conducted at screening and every 9 weeks until the end of treatment. Other scans (mammogram, bone scan) were also used for per investigator discretion. The extra-CNS ORR was evaluated using RECIST version 1.1.[23] Safety and tolerability were assessed at each study visit according to the NIH-NCI CTCAE version 4.03.

Statistical analysis

The primary endpoint was a 12-week CNS ORR. Standard systemic therapy was associated with a CNS response rate of 20% (P0).[8] Assuming an ORR for investigational combination was 35% (P1), 47 participants would be required to detect a difference with 80% power, and a 0.05 significance level using a one-sided Chi-square test. Due to slow accrual and restricted funding, the study closed after enrollment of 19 participants. Statistical analysis based on an intention-to-treat (ITT) approach was performed at the end of the study. Under this approach, analysis for the primary endpoint was based on all eligible participants who underwent

an MRI at the 12-week timepoint and was estimated with a 95% confidence interval (CI). Participants' baseline clinical characteristics were summarized using descriptive statistics. Safety analysis included all participants who enrolled and received at least one dose of study treatment. AEs were tabulated by body system, severity and relation with study treatment. Common toxicities (experienced by $\geqslant$10% of participants) were also identified. PFS and OS distributions were estimated using a Kaplan–Meier product limit method and survival curves for PFS and OS were plotted. Median PFS, median OS (and corresponding 95% CI) were obtained. Fisher's exact tests were performed to evaluate the association between CNS ORR and HR status, with prior brain radiation [stereotactic radiosurgery (SRS) and whole brain irradiation (WBI)] or prior brain surgery, with prior lapatinib or prior capecitabine. Similarly, log-rank tests were used to assess the association between PFS and these variables. For all statistical investigations, tests for significance were two-tailed. A p-value less than the 0.05 significance level was considered to be statistically significant. All statistical analyses were carried out using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Participant characteristics

From 7 June 2013 to 4 January 2016, 21 participants were screened and 19 participants were enrolled and treated with at least one dose of study drug (10 in phase Ib, 9 in phase II) at 11 centers in the US (Figure 1). Baseline participant characteristics are shown in Table 1 and patient disposition and prior treatments received are shown in Table 2. All participants were evaluable for safety and secondary outcome measures. Participants had received a median of 2.5 (0–11) prior systemic therapies for MBC including lapatinib or capecitabine in 14 (74%); 3 had prior lapatinib but not capecitabine, 2 had prior capecitabine but not lapatinib, and 9 had prior capecitabine and lapatinib. Additionally, 12 participants (63%) had prior CNS radiotherapy or surgery and radiation (9 had radiation only and 3 had both surgery and radiation). Of the 12 patients who had prior CNS radiation, 2 had stereotactic radiosurgery only, 5 had whole brain radiation only and 5 had both whole brain radiation and stereotactic radiosurgery (see Table 2). At baseline, eight participants (63%) had measurable extra-CNS metastatic disease.

Phase Ib dose-escalation phase

A total of 10 study participants were enrolled and treated in the dose-escalation phase of the trial: 3 in cohort 1, 4 in cohort 2, and 3 in cohort 3. Of the participants enrolled in cohort 2, one did not receive the study treatment per protocol, thus after receiving Data Safety Monitoring Board approval, a fourth participant was enrolled in this cohort. No DLTs were observed in any of the three cohorts.

In cohort 3, one participant experienced a serious adverse event (SAE) of grade 3 cellulitis, which was not a DLT-based on the protocol definition, given its onset outside the observation window for DLTs (during cycle 1). The MTD was established at the cohort 3 dose level. However, given the need for dose reductions due to toxicity after cycle 1 in cohort 3, cohort 2 dose levels were used in the phase II expansion portion of the study. A total of nine participants were enrolled in the phase II portion and received capecitabine (750 mg/m^2), everolimus (10 mg) and lapatinib (1000 mg).

Safety

The safety results are summarized in Table 3. SAEs were reported in seven (36.8%) participants, including radiation necrosis, catheter-related infection, cellulitis, confusion, dehydration, hyperglycemia, mucositis, pleural effusion, pneumonia (n = 2), pulmonary embolism, and weakness/lethargy. Overall there were 12 grade 3/4 treatment-emergent adverse events (TEAEs), all of which were grade 3 with the exception of one grade 4 hypokalemia and one grade 4 fever. The most common grade 3/4 TEAEs were oral mucositis (n = 3, 16%), hypokalemia, fatigue, and diarrhea (n = 2, 11% for each). Prophylactic use of steroid mouthwash was not required nor was it used by any patient in this trial as this study predated the standard use of prophylactic mouthwash. One patient had grade 3 hyperglycemia. She was taking dexamethasone 2 mg daily for her history of seizures and dizziness which, in addition to the known effects of everolimus on glucose metabolism, may have contributed to this event. No deaths occurred on treatment. Overall, three deaths occurred during the 30-day follow up after the last dose of study drugs due to PD.

Table 1. Baseline patient characteristics ($n = 19$).

Age (mean)	58.5
Hormone receptor status	
ER–/PgR–	7 (36.8%)
ER+/PgR–	5 (26.3%)
ER–/PgR+	1 (5.2%)
ER+/PgR+	6 (31.6%)
Previous therapy for metastatic disease	
No prior therapy	2 (10.5%)
1 line of treatment	1 (5.2%)
2 lines of treatment	7 (36.8%)
⩾3 lines of treatment	9 (47.4%)
Median no. of lines	2.5 (0–11)
ECOG performance status	
0	4 (21.1%)
1	12 (63.2%)
2	3 (15.8%)
Median # of CNS progressions prior to study (range)	2 (0–5)
Measurable extra-CNS disease at baseline	8 (42.1%)

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor.

Primary objective outcomes

A total of 11 eligible participants completed four cycles of treatment, underwent brain MRI at 12 weeks and were evaluable for the primary efficacy outcome of the 12-week CNS ORR. Of these, three participants (27%) had previously received lapatinib and capecitabine, three (27%) had received lapatinib but no prior capecitabine, and two (18%) had received capecitabine but no prior lapatinib (see Table 4).

The 12-week CNS ORR was 27% with three participants showing a PR at 12 weeks (95% CI, 3.6–41.4). All responding patients were started with the same drug doses (capecitabine 750 mg/m^2, everolimus 10 mg and lapatinib 1000 mg). One of these participants had advanced estrogen and progesterone receptor (ER/PgR)-positive disease and had received two previous lines of systemic treatment in the metastatic setting, including lapatinib as well as CNS SRS and WBI. She came off the treatment for noncompliance after 19 cycles. The second participant had no prior CNS radiation and four previous lines of therapy for metastatic disease (including capecitabine). She came off the treatment for CNS progression after 13 cycles. The third participant had prior surgical resection of CNS metastases and three previous lines of therapy in the metastatic setting (including lapatinib). She came off the study after 30 cycles due to CNS progression. Both the second and third participants had HR-negative disease with measurable extra-CNS disease at baseline, and both achieved PR in their extra-CNS ORR. Images from the baseline and 12-week MRIs from the three patients who achieved a response are shown in Figure 2.

Table 2. Patient disposition and prior treatment history.

	Phase Ib ($n = 10$)	Phase II ($n = 9$)	Total ($n = 19$)
Off treatment reason			
Disease progression	9	6	15
• *CNS*	*6*	*5*	*11*
• *Extra-CNS*	*2*	*1*	*3*
• *Both*	*1*	*0*	*1*
Consent withdrawal	0	2	2
Noncompliance	1	1	2
Prior treatment history			
Prior lapatinib/capecitabine			
• *Lapatinib (no capecitabine)*	*1*	*2*	*3*
• *Capecitabine (no lapatinib)*	*2*	*0*	*2*
• *Both*	*5*	*4*	*9*
Prior CNS radiation/surgery			
• *Rad only (SRS/WB/both)*	*(0/3/1)*	*(1/1/3)*	*9*
• *Surgery only (no radiation)*	*0*	*0*	*0*
• *Both radiation and surgery (SRS/WB/both)*	*(1/1/1)*	*(0/0/0)*	*3*

CNS, central nervous system; SRS, stereotactic radio surgery; WB, whole brain.

Secondary objective outcomes

A total of 19 participants were eligible for evaluation of PFS and OS. Overall, three participants were censored from the PFS analysis: two withdrew consent and one was noncompliant. The median PFS was 6.2 months (95% CI, 3.2–9.1) and median OS was 24.2 months (95% CI, 6.2–25.4) (Table 5).

CNS ORR was defined as the best response attained at any time on study. In addition to the three PRs noted, one additional participant attained a CNS PR and one attained a CNS CR after 12 weeks. Thus, the CNS ORR (ITT) was 26% (5/19). Of 19 patients, 9 (47%) participants had stable CNS disease as their best response. One participant (not counted as having a response) was found to be ineligible after enrollment (she received CNS radiation to the target brain lesion without progression in the CNS prior to enrollment). Accounting for this, the CNS ORR in eligible participants is 28% (5/18). One participant with HR+ disease with stable disease at the 12-week timepoint achieved a CNS PR at cycle 6. Prior treatment included four lines of systemic therapy including lapatinib and capecitabine as well as whole brain and gamma knife radiation. Her disease progressed at cycle 9. Another participant with HR+ breast cancer previously treated with lapatinib as well as SRS and WBI who had stable disease at 12 weeks went to surgery at cycle 13 for possible progression of CNS metastasis. Resection pathology revealed no viable tumor, only necrosis. Thus, she achieved a CR. She came off the study at cycle 19 for noncompliance (without PD).

The extra-CNS ORR (ITT) was 10.6% (2/19). Both responses were partial and both participants also achieved a PR in the CNS. Of 19 participants, 8 had measurable extra-CNS disease at baseline. Of these, two (25.0%) achieved a PR, five (63%) had stable disease, and one participant (13%) had PD as their best extra-cranial response.

Table 3. Treatment-related adverse events.

Adverse event	Grade 1/grade 2				Total # pts (%)	Grade 3/grade 4				Total # pts (%)
	Cohort 1 ($n = 3$)	Cohort 2 ($n = 4$)	Cohort 3 ($n = 3$)	Phase II ($n = 9$)		Cohort 1 ($n = 3$)	Cohort 2 ($n = 4$)	Cohort 3 ($n = 3$)	Phase II ($n = 9$)	
Diarrhea	1	2	1	7	11 (57.9%)	1	1	0	0	2 (10.5%)
Mucositis oral	0	1	3	6	10 (52.6%)	0	0	2	1	3 (15.8%)
Fatigue	2	1	1	3	7 (36.8%)	0	0	0	2	2 (10.5%)
Nausea	0	1	0	5	6 (31.6%)	0	0	0	0	0
AST increased	0	0	3	2	5 (26.3%)	0	0	0	0	0
Edema limbs	0	2	2	1	5 (26.3%)	0	0	0	0	0
Hyperglycemia	0	0	2	3	5 (26.3%)	0	0	1	0	1 (5.3%)
Lipid abnormality	0	1	1	2	4 (21.1%)	0	0	0	0	0
ALT increased	0	0	2	2	4 (21.1%)	0	0	0	0	0
Abdominal pain	0	1	1	1	3 (15.8%)	0	0	0	0	0
Rash acneiform	1	1	1	0	3 (15.8%)	0	0	0	0	0
Vomiting	0	0	0	3	3 (15.8%)	0	0	0	0	0
Blood bilirubin increased	0	0	1	1	2 (10.5%)	0	0	0	0	0
Dehydration	1	0	1	0	2 (10.5%)	0	0	0	1	1 (5.3%)
Fever	0	0	0	2	2 (10.5%)	0	0	0	1	1 (5.3%)
Headache	1	0	0	1	2 (10.5%)	0	0	0	0	0
Hoarseness	1	0	1	0	2 (10.5%)	0	0	0	0	0
Hypokalemia	0	0	2	0	2 (10.5%)	0	0	1	1	2 (10.5%)
Dermatologic disorders	0	1	1	0	2 (10.5%)	0	0	0	0	0
Weight loss	0	0	0	2	2 (10.5%)	0	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4. Primary endpoint CNS objective response rate at 12 weeks*.

	Phase Ib ($n = 5$)	Phase II ($n = 6$)	Total ($n = 11$)
Objective response rate, *n* (%)	2 (40.0%)	1 (16.7%)	3 (27.3%)
Complete response	0	0	0
Partial response	2	1	3

*Evaluable population included eligible patients who received four cycles of treatment and underwent imaging of the brain at week 12.
CNS, central nervous system.

Table 5. Secondary endpoints.

	Phase Ib ($n = 10$)	Phase II ($n = 9$)	Total ($n = 19$)
CNS objective response rate, n (%)[a]	3 (30)	2 (22)	5 (26)
Complete response	*0*	*1 (11)*	*1 (6)*
Partial response	*3 (30)*[b]	*1 (11)*	*4 (22)*
Stable disease	*3 (30)*	*6 (67)*	*9 (47)*
Clinical benefit rate, *n* (%)	4 (40)	4 (44)	8 (42)
	Phase Ib ($n = 4$)	**Phase II ($n = 4$)**	**Total ($n = 8$)**
Extra-CNS objective response rate, *n* (%)[c]	1 (25)	1 (25)	2 (25)
Complete response	*0*	*0*	*0*
Partial response	*1 (25)*	*1 (25)*	*2 (25)*
Stable disease	*2 (50)*	*3 (75)*	*5 (63)*
Median PFS, months (95% CI)	4.6 (1.2, 9.1)	6.3 (0.5, 20.9)	6.2 (3.2, 9.1)
Median OS, months (95%)	12.1 (5.2, 25.4)	NR (2.1, NR)	24.2 (6.2, 25.4)

[a]CNS ORR, all 19 treated patients included in intent to treat analysis, however 1 patient was later found to be ineligible as she had received CNS radiation to the sole target brain lesion. Her results are not included as a response.
[b]One patient achieved response after 12 weeks and was not included in primary endpoint of CNS ORR at week 12.
[c]Only patients with measurable extra-CNS lesions at screening were included.
CI, confidence interval; CNS, central nervous system; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

No significant associations were found when comparing CNS ORR by HR status, prior brain radiation or surgery, or with prior lapatinib or prior capecitabine. Similarly, no significant associations were found using these comparisons for PFS (all p-values >0.05).

Discussion

There are limited therapeutic options for patients with trastuzumab-refractory, HER2+ breast cancer who develop CNS disease after cranial surgery/radiotherapy. As the survival of these patients continues to improve, the need for effective salvage therapies will increase.[24] While consensus guidelines from the American Society of Clinical Oncology for treating HER2+ CNS metastases include surgical resection with postoperative radiation, SRS, and WBI,[25] trials that evaluate novel systemic therapies and innovative treatment combinations are desperately needed.

Several studies have been conducted to evaluate the activity of lapatinib plus capecitabine for HER2+ CNS metastases.[8,26–31] Responses were reported in two clinical trials evaluating lapatinib

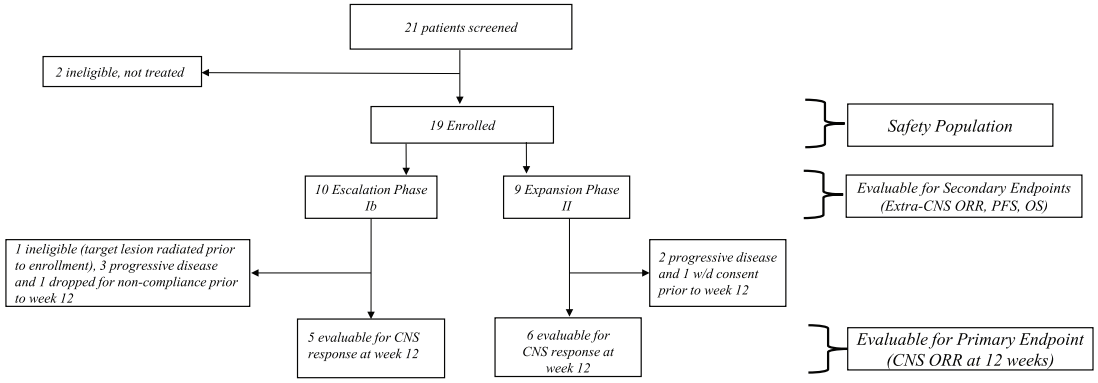

Figure 1. Consort diagram.

plus capecitabine that enrolled patients who were not heavily pretreated. A phase II trial reported an ORR of 33.3% (7/21 all PR) and median PFS of 5.5 months in patients with HER2+ MBC with CNS involvement previously treated with trastuzumab.[26] Cranial radiation had been given to 16 of the 21 participants prior to enrollment. The ORR was 31.2% (5/16) in patients who received prior cranial therapy and 40% (2/5) in patients who were receiving first-line treatment. Another phase II trial investigated lapatinib plus capecitabine *versus* lapatinib plus topotecan for patients with HER2+ BCBM and demonstrated an ORR of 38% in the lapatinib plus capecitabine arm.[28] In the phase II LANDSCAPE study, 65.9% (29/44) of the patients achieved a PR with lapatinib and capecitabine for their previously untreated brain metastases.[29] All three studies restricted enrollment to patients with no previous exposure to lapatinib or capecitabine.

Lapatinib plus capecitabine has also been evaluated in more heavily pretreated patients in a study led by Lin and colleagues. In this study, patients with BCBM whose disease progressed on lapatinib ($n = 50$)[8] were allowed to continue on the study and add capecitabine. This regimen was associated with a 20% CNS ORR (all PR) and a median PFS of 3.65 months. In contrast, our study allowed patients to enroll who had previously received lapatinib or capecitabine. The majority of our patients had previously received capecitabine ($n = 11$, 58%) or lapatinib ($n = 12$, 63%).

Preclinical studies show that the PI3K pathway is uniquely active in BCBM, thus inhibition of this pathway represents a promising therapeutic option for these patients. Specifically, inhibition of PI3K and mTORC1 in patient-derived xenografts of HER2+ BCBM resulted in marked tumor regression mediated by significant reductions in p-S6RP and p-4EBP1 and significant decreases in Ki67 staining.[32,33] A phase II study investigating the treatment of HER2-positive, progressive BCBM with everolimus, vinorelbine, and trastuzumab, reported a CNS ORR of only 4% but an OS of 12.2 months with a 27% clinical benefit rate at 6 months (ClinicalTrials.gov identifier NCT01305941).[34]

To our knowledge, ours is the first prospective study reported to evaluate the combination of lapatinib and capecitabine plus everolimus for BCBM. Our study revealed that this regimen is generally well tolerated in patients and demonstrates clear evidence of antitumor activity in very heavily pretreated patients with HER2+ BCBM with a CNS ORR of 27% at 12 weeks and a PFS of 6.2 months. Interestingly, two responding patients had previously been treated with lapatinib and one had previously received capecitabine. Moreover, this regimen seems to have a comparable observed effect outside the CNS.

One strength of this study is the utilization of a single radiologist reviewer of all MRI scans, thus CNS ORR was based on central assessment. This study had several limitations. First, accrual goals were not met, resulting in a small sample size in the phase II portion. Second, the lack of a control arm precludes a comparison from being made to other options commonly used for progressing CNS metastases, namely capecitabine and lapatinib. In addition, prior radiotherapy or surgical treatment may have influenced the observed response to therapy by altering the permeability of the blood–brain barrier or otherwise affecting the tumor microenvironment. That said, other

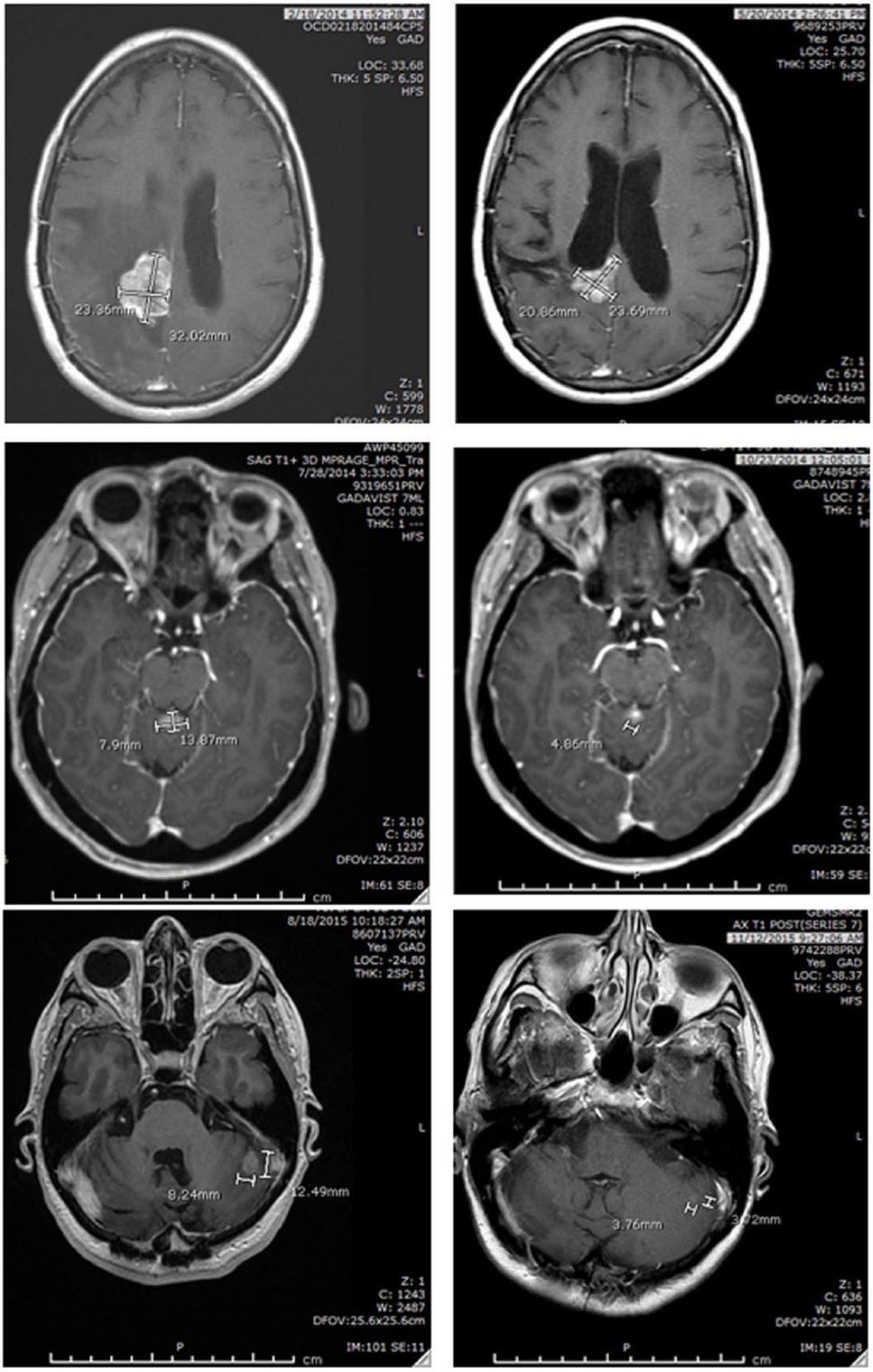

Figure 2. Magnetic resonance imaging showing partial response in three patients at the 12-week timepoint. Left panel: baseline; right panel: 12 weeks after therapy.
All patients initiated therapy with capecitabine 750 mg/m^2, everolimus 10 mg and lapatinib 1000 mg.

studies that included patients who had not had local therapy yielded higher CNS ORR.[29,30] This study would have been strengthened by inclusion of a patient-reported quality of life metric. Lastly, there was variability regarding prior exposure to lapatinib or capecitabine among our patient population which made it challenging to fully ascertain the effect of everolimus on treatment efficacy. While one of the patients who achieved CNS PR at 12 weeks had been treated with both lapatinib and capecitabine, we cannot be certain that the other patients who showed a response was due entirely to everolimus, as they were treated with two new drugs.

Conclusion

In summary, the novel triplet therapy combination of lapatinib, everolimus, and capecitabine has been shown to be well tolerated with regression of BCBM in over a quarter of patients with trastuzumab-refractory, heavily pretreated disease. While everolimus shows promising activity in the CNS, further studies are needed to better understand its role in CNS metastases.

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Conflict of interest statement

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