# Afatinib as a single agent or in combination with vinorelbine versus investigator's choice of treatment in HER2-positive breast cancer with progressive brain metastases after trastuzumab and/or lapatinib-based therapy (LUX-Breast 3): a randomised phase 2 trial

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**Previous presentation:** Presented in part at the San Antonio Breast Cancer Symposium, December 9–13, 2014, San Antonio, USA

## Summary

**Background** Patients with advanced HER2-positive breast cancer frequently develop central nervous system (CNS) metastases. Metastases that progress following brain radiotherapy and HER2-targeted systemic therapy are a difficult therapeutic challenge. We aimed to assess the efficacy and safety of single-agent afatinib, afatinib plus vinorelbine or a regimen of investigator's choice in women with HER2-positive breast cancer with progressive brain metastases during or after trastuzumab and/or lapatinib therapy.

**Methods** Women with HER2-overexpressing breast cancer with measurable CNS recurrence/progression detected during or after trastuzumab and/or lapatinib-based therapy were eligible for this randomised, open-label, multicentre, phase 2 trial. Patients were randomised centrally using a validated random number generator and a block size of six, stratifying for Eastern Cooperative Oncology Group performance status, number of brain metastases at screening and prior lapatinib treatment, in a 1:1:1 ratio to receive afatinib, an irreversible ErbB family blocker, 40 mg orally once daily (Group A), afatinib 40 mg daily plus weekly intravenous vinorelbine 25 mg/m$^2$ (Group B), or investigator's choice of treatment (Group C). The primary endpoint, assessed in the intention-to-treat population, was patient benefit at 12 weeks, defined by an absence of cancer progression, no worsening of neurological signs and symptoms and no increase in corticosteroid dosage. This completed trial is registered with ClinicalTrials.gov, NCT01441596.

**Findings** Between Dec 22, 2011 and Feb 12, 2013, 132 patients were screened and 121 were randomised. Most (83·5%) had received prior brain radiotherapy. The primary endpoint was achieved in 12 (30·0%), 13 (34·2%), and 18 (41·9%) of the 40, 38, and 43 patients assigned to Groups A, B, and C, respectively (Group A *vs* C, p=0·37; Group B *vs* C, p=0·63). Treatment-related grade 3 or 4 adverse events (AEs) were frequent (Group A, 21 [53%] of 40; B, 30 [81%] of 37; C, nine [21%] of 42 patients). Diarrhoea was the most common grade 3/4 AE in Group A (seven [18%]) and neutropenia was the most common grade 3/4 AE in Groups B and C (14 [38%] and four [10%], respectively). Treatment-related serious AEs occurred in five (13%) patients in Group A, 11 (30%) in Group B and two (5%) in Group C.

**Interpretation** Clinical anti-tumour activity with afatinib-containing treatments was not different from investigator's choice treatments; however, adverse events were frequent and afatinib-containing treatments appeared to be less well tolerated. The findings suggest that some patients with brain metastases progressing during HER2-targeted treatment benefit from continuation of HER2-targeting therapy.

**Funding** Boehringer Ingelheim.

## Introduction

Up to 50% of patients with advanced HER2-positive breast cancer are diagnosed with brain metastases during the course of the disease.[1] Although the introduction of HER2-targeted agents, such as trastuzumab, has improved outcomes, survival times for breast cancer patients with brain metastases are still relatively short: approximately 2 years following the first detection of metastatic lesions.[2–4] Local therapies, including whole brain irradiation or stereotactic radiation therapy, surgery, or combinations thereof, are the current standard of care for brain metastases. At present, there are no systemic therapies specifically approved for the treatment of breast cancer patients with brain metastases.[1] However, in a phase 2 trial the HER2/epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, lapatinib plus capecitabine, demonstrated substantial activity in HER2-positive breast cancer patients who had brain metastases but had not received whole brain radiotherapy. Objective response was achieved in 29 (65·9%) of 45 patients; however, 22 (49%) of patients experienced grade 3/4 treatment-related adverse events (AEs).[5]

Patients whose brain metastases progressed despite radiation therapy and a regimen that includes a HER2-targeting agent, such as trastuzumab or lapatinib, pose a difficult therapeutic challenge. Lapatinib monotherapy demonstrated modest activity in patients with progressive HER2-positive brain metastases after radiotherapy and trastuzumab;[6,7] however, no randomised phase 2/3 trials are available to guide selection of systemic treatments in breast cancer patients with progressive brain metastases after initial therapy, and it is currently unknown whether such treatments influence survival.[1]

Afatinib is an oral, irreversible ErbB family blocker.[8] In a phase 2 trial, afatinib demonstrated activity in patients with metastatic HER2-positive breast cancer previously treated with trastuzumab and chemotherapy.[9] In preclinical studies, the antitumour activity of afatinib was increased by adding vinorelbine. This combination also demonstrated activity in phase 1 trials in patients with advanced solid tumours,[10,11] and was thus taken forward for evaluation in phase 3. While in phase 3 development for breast cancer,[12] afatinib also showed activity in patients with brain metastases and other tumour types.[13] Although the ability of afatinib to cross the blood-brain barrier has not been thoroughly investigated, this clinical data indicated that afatinib could traverse the blood-brain barrier sufficiently to elicit antitumour activity in patients with breast cancer brain metastases. Furthermore, as afatinib, unlike lapatinib and trastuzumab, is an irreversible inhibitor of HER2,[14] we hypothesised that afatinib might be effective in patients with brain metastases that had progressed on these agents. In the present hypothesis-generating, randomised study we treated women with HER2-positive breast cancer with progressive brain metastases during or after trastuzumab and/or

lapatinib-based therapy either with single-agent afatinib, afatinib plus vinorelbine, or a regimen of investigator's choice. To our knowledge, the present study is the largest randomised trial conducted in this setting and a similar study has not been conducted before.

## Methods

### Study design and patients

This randomised, open-label, multicentre, phase 2 trial was performed at 40 centres across Canada, Finland, France, Germany, Italy, Spain, South Korea, and the USA. Women aged ≥18 years with histologically confirmed HER2-overexpressing breast cancer as per local assessment, with central nervous system (CNS) recurrence/progression as determined by Response Evaluation Criteria in Solid Tumors (RECIST) during or after trastuzumab- and/or lapatinib-based therapy, were eligible to participate. Other inclusion criteria comprised the presence of at least one measurable and progressive lesion in the CNS (≥10 mm on T1-weighted, gadolinium-enhanced magnetic resonance imaging [MRI]) after prior systemic and/or radiation therapy, an Eastern Cooperative Oncology Group performance score (ECOG PS) of 0–2 and life expectancy of ≥3 months. Key exclusion criteria were prior treatment with a HER2-tyrosine kinase inhibitor other than lapatinib; HER2 inhibitor treatment within 14 days (trastuzumab and other antibodies) or 7 days (lapatinib) of study start; surgery within 4 weeks, radiotherapy, stereotactic radiosurgery, chemotherapy, or investigational therapy within 14 days, or hormonal therapy within 7 days prior to study start; pre-existing interstitial lung disease, and significant gastrointestinal disorders with diarrhoea as a major symptom. Patients with leptomeningeal carcinomatosis as the only site of CNS metastases were not eligible. Additionally, patients were excluded if they had an absolute blood neutrophil count <1.5 x $10^9$ cells per L, platelet count <100 x $10^9$ cells per L, calculated serum creatinine clearance <60 mL/min or serum creatinine >1.5 x upper limit of normal (ULN), bilirubin >1.5 x ULN, or aspartate aminotransferase or alanine aminotransferase concentration >3 x ULN (if related to liver metastases, >5 x ULN).

The protocol was approved by local Institutional Review Boards/Ethics Committees and the study was conducted in compliance with the International Conference on Harmonization Good Clinical Practice. Patients provided written informed consent.

## Randomisation and masking

Patients were randomised (1:1:1) to receive afatinib alone (Group A), afatinib and vinorelbine (Group B), and investigator's choice of treatment (Group C). Stratification was performed according to ECOG PS (0–1 *vs* 2), number of brain metastases at screening (≤3 *vs* >3) and prior treatment with lapatinib (yes *vs* no). A block size of six was used and randomisation was done centrally at Boehringer Ingelheim using a validated random number generator and implemented using an Interactive Voice/Web Response System.

Treatment assignment was not masked for clinicians, patients or those who analysed the data owing to the different administration schedules in each arm. To reduce bias, the trial was conducted in a blinded manner by the sponsor trial team, until database lock. An Independent Data Monitoring Committee team met every 6 months to monitor the safety of patients and evaluate the benefit-risk ratio. A benefit-risk analysis was performed when 20 patients had been treated in each treatment arm to determine whether to proceed with the trial or stop one of the treatment arms for futility.

## Procedures

For Group A, the initial dose of afatinib was 40 mg once daily (as this was the standard monotherapy dose for phase 3 trials); however, this could be increased to 50 mg from cycle 2 onwards if the patient did not have diarrhoea, skin-related AEs or mucositis or any grade ≥2 drug-related AE. If patients had any grade ≥3 drug-related AEs, or grade 2 diarrhoea lasting ≥2 days, or nausea or vomiting for ≥7 consecutive days despite best supportive care, or grade ≥2 worsening of renal function, then afatinib was paused for up to 14 days until recovery to grade 1 or 0 or to the baseline level. Afatinib then was resumed at a lower dose (10 mg decrements to a minimum dose of 20 mg). In Group B, patients received afatinib 40 mg once daily plus vinorelbine 25 mg/m$^2$ administered as a weekly intravenous infusion. Afatinib dose reductions were performed in case of AEs (as detailed above) and vinorelbine doses could be skipped in case of tolerability issues in accordance with the summary of product characteristics (vinorelbine dose reductions to 20 mg/m$^2$ weekly were permitted if deemed necessary by the investigator and the patient was deriving clinical benefit). In Group C, investigator's choice of treatment comprised any chemotherapy and/or medical treatment approved for advanced/metastatic breast cancer (best supportive care alone was not a permitted treatment option). Treatments were administered in accordance with the summary of product characteristics or local treatment guidelines, thus dose reductions were not anticipated for these agents. In all three study groups, concomitant medications could be

administered as clinically required (eg, corticosteroids, bisphosphonates, anticonvulsants, palliative radiotherapy for non-target lesions). Palliative radiotherapy was permitted due to the late-stage setting of this trial. Growth factor support was also permitted.

Treatment was administered in 3-week cycles until disease progression (CNS or extra-CNS lesions), unacceptable AEs, or withdrawal of consent.

Tumour assessment was performed with gadolinium-enhanced MRI of the brain and computed tomography of the chest and abdomen at screening, every 6 weeks for the first 12 weeks, and then every 9 weeks until disease progression, death, or last follow-up. Neurological symptoms were assessed by the investigator using the Neurological Examination Worksheet and assessed at screening and at each tumour assessment. A decline of ≥2 Common Terminology Criteria for Adverse Events (CTCAE) v3·0 levels for ≥7 days for a neurological sign or symptom was considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. AEs were graded according to CTCAE v3.0. Patients were followed up for safety 28 days after discontinuing study therapy and, every 6 to 9 weeks thereafter until disease progression or start of further treatment. They were then followed-up every 60 days, by patient records, phone, or visit until death or end of trial.

## Outcomes

The primary endpoint, assessed by the investigator, was patient benefit at 12 weeks after the date of randomisation based on the following criteria, each of which had to be fulfilled: absence of CNS disease progression according to Response Evaluation Criteria in Solid Tumors version 1·1, no tumour-related worsening of neurological signs/symptoms, no increase in corticosteroid dosage, and no progression of extra-CNS disease.

Secondary endpoints included progression-free survival (PFS; time from randomisation to disease progression in either CNS or extra-CNS lesions or death, whichever occurred first) and overall survival (OS; time from randomisation to death from any cause). Other endpoints included best overall response rate (ORR) in CNS and extra-CNS lesions (assessed by investigators according to RECIST version 1.1), and safety. Duration of response was calculated from the date of first documented complete response (CR) or partial response (PR) to the date of progression or death, whichever occurred first.

## Statistical analysis

This was an exploratory trial and, as such, there was no formal sample size calculation. However, assuming clinical benefit rates of 35% for Group A, 40% for Group B, and 25% for Group C, a sample size of 40 patients per arm would be required for a 80% probability of correctly preferring Group A versus Group C, and for a 90% probability of correctly preferring Group B versus Group C, using Simon's selection criteria.[15]

Efficacy analyses were performed using the intention-to-treat (ITT) population including all randomised patients. For the analysis of patient benefit, Clopper-Pearson 95% confidence intervals (CIs) were calculated for proportion of patients with clinical benefit in each study group, and for between-group differences (Group A *vs* Group C and Group B *vs* Group C); differences between groups were compared using the Wald asymptotic test with a continuity correction. Survival was analysed using the Kaplan–Meier life-table method. Survival between groups was compared with the likelihood score test; hazard ratios were computed using a univariate Cox model, and Greenwood's variance estimate used to determine CIs. The Wald test was used to verify that the proportionality assumption was valid. Given the exploratory nature of these analyses, all reported confidence intervals and p-values should be regarded with caution. The safety population comprised all patients receiving one or more doses of study medication.

Statistical analyses were done with SAS (version 9·2). The study is registered with ClinicalTrials.gov, NCT01441596.

## Role of the funding source

The funder provided the study drug, and was involved in trial design in collaboration with HJ. The funder also had a role in collection of data through management of the clinical trial database and analysed the data according to the statistical plan. HJ had full access to the study data and prepared the Article draft. All authors, in collaboration with the funder, interpreted the data and were involved in manuscript development. Professional medical writers, supported financially by the funder, assisted the authors with article development. All authors approved the final version of the manuscript and made the final decision to submit the report for publication.

# Results

## Patients and treatment exposure

Between 22 December 2011 and 12 February 2013, 132 patients were screened; 121 were randomised and 119 received study medication (figure 1). Demographics and baseline characteristics were generally well balanced across the groups (table 1). The majority of patients had more than three brain metastases and were heavily pre-treated: 82 (68%) of 121 patients had received >2 prior chemotherapy regimens, 101 (84%) prior brain radiotherapy, 121 (100%) prior trastuzumab, and 95 (79%) prior lapatinib. All patients had discontinued study treatment before data collection cut-off (figure 1). No patients had palliative radiotherapy prior to disease progression during the trial.

Median duration of treatment was 10·2 weeks (interquartile range [IQR] 6·0–17·3) in Group A (afatinib monotherapy), 11·4 weeks (IQR 6·1–21·0) in Group B (afatinib–vinorelbine), and 12·6 weeks (IQR 5·1–21·9) in Group C (investigator's choice); median numbers of treatment courses completed were 3·5, 4·0, and 4·0, respectively. In all three groups, disease progression (either confirmed or in 10 cases detected clinically without imaging) was the most common reason for stopping treatment (figure 1). Treatments administered in Group C were: trastuzumab plus chemotherapy (22 patients, 11 of whom received trastuzumab plus vinorelbine); trastuzumab plus lapatinib plus chemotherapy (three patients); lapatinib plus chemotherapy (10 patients); lapatinib alone (one patient), or chemotherapy alone (six patients; table S1).

## Efficacy

The primary endpoint, patient benefit at 12 weeks, was achieved in 12 (30%) of 40 patients in Group A, 13 (34%) of 38 patients in Group B, and 18 (42%) of 43 patients in Group C (table 2; p=0.37 for Group A *vs* C, and p=0.63 for Group B *vs* C). Median PFS was 11·9 weeks (95% CI 6·3–18·7) in Group A, 12·3 weeks (7·4–17·3) in Group B, and 18·4 weeks (11·1–21·1) in Group C (table 2; figure 2A). Progression by site (CNS lesions, extra-CNS lesions or both) is detailed in table 3. Median OS was 57·7 weeks (95% CI 39·3–68·1) in Group A, 37·3 weeks (25·3–57·3) in Group B, and 52·1 weeks (39·3–80·4) in Group C (table 2; figure 2B). The proportionality assumptions of the Cox models used to calculate the HRs were valid (for PFS, p=0.70; for OS, p=0.22).

The waterfall plot of maximum decrease from baseline in the sum of longest diameters of CNS target lesions is shown in figure 3. Objective response rates were below 10%, except for CNS lesions in Group C (six of 43 patients, 14%). In Group C, CNS responses were observed in two patients receiving trastuzumab plus chemotherapy and four receiving lapatinib plus chemotherapy. Extra-CNS responses were observed in patients receiving lapatinib plus capecitabine. Disease control rates (CR, PR, or stable disease for ≥6 weeks) were similar for CNS lesions in all groups (table 2).

## Safety

The most frequent (>20%) treatment-related AEs (any grade) were: diarrhoea, rash, and asthenia in Group A; diarrhoea, rash, neutropenia, mucosal inflammation, nausea, stomatitis, anaemia, and asthenia in Group B; and diarrhoea, neutropenia and asthenia in Group C (table 4). Grade 3/4 AEs occurred in 21 (53%) of 40 patients, 30 (81%) of 37 patients, and nine (21%) of 42 patients in Groups A, B, and C, respectively (table 4). Diarrhoea was the most common Grade 3/4 AE in Group A and was also frequently reported in Group B (occurring in seven [18%] patients in Group A, nine [24%] patients in Group B and two [5%] patients in Group C). Haematological disorders occurred as treatment-related AEs in Groups B and C more frequently than in Group A (table 4). Neutropenia was the most common Grade 3/4 AE in Groups B and C (occurring in 14 [38%] and four [10%] patients, respectively; no patients in Group A experienced neutropenia).

Treatment-related serious AEs were reported in five (13%) of 40 patients in Group A (decreased appetite, diarrhoea, vomiting, stomatitis, nausea, acute renal failure, general physical health deterioration); 11 (30%) of 37 patients in Group B (lung infection, urosepsis, febrile neutropenia, anaemia, partial seizures, diarrhoea, vomiting, dysphagia, enteritis, stomatitis, rash, asthenia, mucosal inflammation, pyrexia), and two (5%) of 42 patients in Group C (febrile neutropenia and diarrhoea). There were no treatment-related deaths; however, three (8%) patients in Group A, seven (19%) in Group B, and five (12%) in Group C had a non-related AE leading to death, primarily due to disease progression. In Group C, one of the 5 patients with an AE leading to death died at home 37 days after the last treatment administration (i.e. lapatinib and capecitabine). This patient had a symptomatic lesion in the rachidian bulb, but no clear signs of disease progression except Grade 2 asthenia. The investigator considered the death as not treatment-related.

AEs leading to dose reduction were observed in 17 (43%) of 40 patients in Group A, 16 (43%) of 37 patients in Group B, and three (7%) of 42 patients in Group C. Diarrhoea was

the most common reason for dose reduction (nine [23%] patients in Group A, 10 [27%] in Group B, and one [2%] in Group C). Neutropenia resulted in dose reduction in four (11%) patients in Group B and in one (2%) patient in Group C. AEs leading to discontinuation of study medication were reported in four (10%) patients in Group A, nine (24%) in Group B, and nine (21%) in Group C.

## Discussion

In LUX-Breast 3, we found that approximately one-third of patients in each treatment group achieved clinical benefit, defined by absence of breast cancer progression at any site for at least 12 weeks with no tumour-related worsening of neurological symptoms and no increase in corticosteroid dosage. The median PFS times ranged from 11·9 weeks in Group A to 18·4 weeks in Group C, and the median OS times from 37·3 weeks in Group B to 57·7 weeks in Group A. Although objective responses in the CNS were infrequent the results suggest that the study treatments had modest activity for brain metastases in this heavily pre-treated population. As context, in a phase 2 trial in patients with HER2-positive metastatic breast cancer which had progressed after trastuzumab treatment, afatinib monotherapy resulted in objective responses in four (10%) of 41 treated patients and median PFS of 15.1 weeks.[9] In the phase 3 LUX-Breast 1 trial in patients with HER2-positive metastatic breast cancer which progressed on or after adjuvant or first-line trastuzumab, objective response occurred in 154 (46%) of 334 afatinib plus vinorelbine-treated patients and median PFS was approximately 24 weeks.[12] Of note, in both of these trials, patients with active brain metastases were excluded. Therefore, the generally lower response rates and PFS in our trial may reflect that brain metastases are difficult to treat. Moreover, the different patient populations enrolled should also be taken into consideration; for example, approximately 40% of patients in the LUX-Breast 1 trial were receiving afatinib plus vinorelbine as first-line treatment for advanced breast cancer while all patients in our trial had received prior treatment for advanced breast cancer.[12]

Most patients experienced disease progression in CNS lesions. This is likely because all patients in this study had to have a documented progression of the CNS lesions and at least one measurable CNS lesion before study entry while the progression or presence of extra-CNS lesions was not required (it is of note that only 41.3% of patients had extra-CNS target lesions). Therefore, some patients may have had stable (or well controlled) extra-CNS lesions at study entry. As such, it may be considered that most of the patients had aggressive/resistant disease in the brain with reduced drug penetration through their blood-

brain barrier leading to frequent progression of the CNS lesions only while the extra-CNS lesions, if present, often remained well controlled.

HER2-targeting agents are commonly continued over several lines of treatment of HER2-positive metastatic breast cancer, since two randomised trials found that continuation of trastuzumab is beneficial in patients whose cancer progresses during a trastuzumab-containing regimen,[16–18] and administration of second anti-HER2 agents may still have substantial efficacy in patients who progress on trastuzumab or other HER2-targeting agents.[19,20] Although there has never been any formal proof that HER2-targeting agents are effective in patients with brain metastases, retrospective analyses suggest that trastuzumab regimens prolong survival of patients with CNS metastases.[21] In order to conclusively demonstrate proof of efficacy of HER2-targeting agents in this setting, afatinib and/or other HER2 targeted agents would need to be compared with a regimen without a HER2-targeting agent. However, similar to others who performed a randomised trial in patients with brain metastases,[22] our trial design did not prohibit use of HER2-targeted agents as this may have been considered unethical and would likely have hindered accrual to the study. Instead we chose to use an investigator's choice regimen as a comparator.

The study was not powered to compare the groups, but the results suggest that single-agent afatinib or afatinib plus vinorelbine did not provide better outcomes than the investigator's choice of treatment. Patient benefit rate was 30%, 34% and 42% in Groups A, B and C respectively. No objective responses were documented in the afatinib monotherapy group in this patient population where most patients had received trastuzumab and lapatinib. As expected, the investigators' choices were heterogeneous in the absence of any approved treatment for this setting, but mostly consisted of trastuzumab and/or lapatinib given with chemotherapy, despite prior cancer progression on trastuzumab and/or lapatinib. The current results do not contradict a hypothesis that some patients may benefit from continuation of a HER2-targeting agent, with the addition of chemotherapy, despite prior progression on this agent. Of note, quality of life was not assessed in this trial and this would be another important endpoint to consider in future evaluations of treatments for patients with breast cancer and brain metastases.

Trastuzumab penetrates poorly through an intact blood-brain barrier. Trastuzumab concentrations achieved in the cerebrospinal fluid (CSF) were 420-times lower than serum concentrations in one study; however, a higher CSF-to-serum ratio of 1:76 was obtained in patients who had received whole brain radiation therapy.[23] Trastuzumab uptake may also be greater in cancerous brain lesions where the blood-brain barrier is impaired. In one study,

patients had 17·5-times higher uptake of $^{89}$Zr-labelled trastuzumab in positron emission tomography in brain metastases versus macroscopically normal brain tissue.[24] Lapatinib does not significantly traverse an intact blood-brain barrier in preclinical models,[25] but has clinical activity for brain metastases.[6,7] Similarly, many chemotherapy agents, including vinorelbine, do not cross an intact blood-brain barrier,[26] but may still have efficacy for breast cancer brain metastases.[27,28]

Afatinib monotherapy is approved for the first-line treatment of patients with EGFR mutation-positive non-small cell lung cancer (NSCLC) and has demonstrated efficacy in NSCLC patients with brain metastases. In a subgroup analysis of the phase 3 LUX-Lung 3 trial, median PFS with afatinib was similar in patients with or without asymptomatic brain metastases (11·1 versus 13·7 months, respectively).[29] In a compassionate-use program with afatinib the median time to treatment failure for patients with pre-treated NSCLC and CNS metastasis (3·6 months) did not differ from a matched group of 100 patients without CNS metastasis.[30] Eleven of the 31 evaluable NSCLC patients had a CNS response to afatinib, and most had cerebral disease controlled. One patient with an impressive response had an afatinib concentration in the CSF of nearly 1 nM.[30] While this concentration is likely sufficient to inhibit EGFR/ErbB1 and HER4/ErbB4, this concentration is below the half maximal inhibitory concentration ($IC_{50}$) for HER2 (14 nM). Thus, the concentration achieved in the CSF in the current study might not have been sufficient to inhibit HER2, and could explain the lower efficacy in HER2-positive breast cancer brain metastases versus EGFR-mutated NSCLC brain metastases.

The frequency of grade 3/4 AEs in the present study was high: 21 (53%) of 40 patients and 30 (81%) of 37 patients treated with afatinib monotherapy and afatinib plus vinorelbine, respectively, had a treatment-related grade ≥3 AE recorded (versus 9 [21%] of 42 patients receiving investigator's choice). Discontinuation of afatinib monotherapy due to AEs was infrequent (four [10%] patients), but 17 (43%) had the dose reduced, compared with only 3 (7%) of the patients assigned to investigator's choice of therapy. This difference is not unexpected as afatinib had a well-described dose reduction protocol, whereas dose reductions for agents used in the investigator's choice, such as trastuzumab, were not foreseen based on their prescribing information. The majority of patients assigned to afatinib monotherapy had diarrhoea and 7 (18%) of 40 patients had grade ≥3 diarrhoea, suggesting that early treatment with loperamide or other agents is important for patients receiving afatinib. Overall, no unexpected AEs were observed and the AEs were generally manageable; however, the investigator's choice regimens appeared to be better tolerated particularly when compared with afatinib plus vinorelbine.

In conclusion, approximately one-third of the patients with brain metastases from HER2-positive breast cancer benefited from the HER2-targeted regimens administered in this heavily pre-treated patient population. No objective responses were obtained with single-agent afatinib, but around one-third of patients did not have breast cancer progression during the first 12 weeks on HER2-targeted therapy. Overall, afatinib-containing treatments did not show better activity than investigator's choice treatments and also appeared to be less well tolerated. No further development of afatinib in HER2-positive breast cancer is currently planned.

## *Panel:* Research in context

### Evidence before this study

We performed a systematic review of the literature published up to Mar 31, 2015, using PubMed. Using search terms of “brain metastases” and “HER2” and “breast cancer”, we reviewed publications reporting phase 2 and 3 trials investigating systemic therapy for patients with brain metastases and HER2-positive breast cancer. We confirmed that there is a high unmet need for patients with brain metastases previously treated with radiotherapy and whose metastases progress during HER2-targeted treatment. No systemic therapies have been specifically approved for treatment of breast cancer brain metastases.

### Added value of this study

To our knowledge, this study is the first trial to compare, in a randomised fashion, afatinib alone or in combination with vinorelbine and investigator’s choice of treatment, in patients with HER2-positive breast cancer with progressive brain metastases after prior trastuzumab and/or lapatinib therapy. We found that approximately one third of patients with HER2-positive metastatic breast cancer likely benefitted from their assigned treatments, based on pre-defined criteria; however, afatinib-containing regimens did not have better activity than investigator-selected treatments, which usually consisted of further trastuzumab or lapatinib combined with chemotherapy. Afatinib-containing regimens also appeared to be less well tolerated than the investigator’s choice regimen.

### Implications of all the available evidence

Brain metastases from HER2-positive breast cancer which progress after radiation therapy and trastuzumab or lapatinib therapy are difficult to treat. The data does not suggest that afatinib-containing treatments have better clinical activity than investigator’s choice; however, the study does support the contention that some patients may benefit from continuation of a HER2-targeting agent.

## Acknowledgments

This clinical research is funded by the sponsor, Boehringer Ingelheim Pharmaceuticals Inc. Editorial assistance, supported financially by Boehringer Ingelheim Pharmaceuticals Inc., was provided by Christine Arris and Caroline Allinson of GeoMed, an Ashfield company, part of UDG Healthcare plc, during the preparation of this article.

## Contributors

AS, MO-K, and HJ were involved in the conception and design of the study. MO-K and HJ were involved in the literature search. VD, JR, TB, ELR, ME, S-BK, AS, JHS, P-LK-L, JT, FP, PB, and HJ were involved in data collection. JC, VD, JR, JB, TB, SH, ME, AS, J-MN, P-LK-L, JT, FP, EC, and PB were involved in patient recruitment. JC, VD, JR, JB, SH, S-BK, AS, J-MN, PB, MO-K, FR, and HJ were involved in data analysis and interpretation. All authors were involved in the drafting and reviewing of the manuscript, and approved the final manuscript for submission.

## Declaration of interests

JC has received personal fees from Roche/Genentech and Celgene for consulting and lectures; Novartis and Eisai for lectures; and MedSIR for ownership interest. VD has received personal fees for advisory board and symposia participation from Roche/Genentech, Novartis and Pfizer. TB has received grants, personal fees and non-financial support from Roche and Novartis. SH has received research funds to her institution from Boehringer Ingelheim, Roche/Genentech, Novartis, Lilly, OBI Pharmaceuticals, Merrimack, PUMA, Biomarin and GlaxoSmithKline; honoraria from Boehringer Ingelheim and Roche/Genentech; and reimbursement of travel fees for meetings from Boehringer Ingelheim, Roche/Genentech, Novartis, Lilly, OBI Pharmaceuticals, and Merrimack. AS has received personal fees for compensation for advice from Roche and Celgene. P-LK-L has received a grant from Boehringer Ingelheim, as indicated in the manuscript. FP has participated in clinical research funded by the sponsor, Boehringer Ingelheim, according to a signed agreement. PB has received a grant to his institution from Novartis; and honoraria from Novartis, GlaxoSmithKline, Bristol-Myers Squibb, Orion and Pfizer. MO-K is an employee of Boehringer Ingelheim. FR is an employee of Boehringer Ingelheim. HJ has received money to his institution and honoraria for consultancy roles from BluePrint

Medicines, Ariad Pharmaceuticals and Orion Pharma. The other authors declared no conflicts of interest.

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# Figures and tables

***Table 1*: Patient characteristics at baseline**

| Characteristic | Group A (afatinib monotherapy) n=40 | Group B (afatinib and vinorelbine) n=38 | Group C (investigator's choice) n=43 | Total N=121 |
|---|---|---|---|---|
| Median age at baseline, years (IQR) | 53 (43–58) | 53 (44–57) | 51 (44–63) | 53 (44–58) |
| Post-menopausal, n (%) | 28 (70) | 29 (76) | 31 (72) | 88 (73) |
| Race, n (%) | | | | |
| White | 21 (53) | 19 (50) | 20 (47) | 60 (50) |
| Asian | 6 (15) | 6 (16) | 6 (14) | 18 (15) |
| Black/African American | 1 (3) | 0 | 0 | 1 (1) |
| Not recorded* | 12 (30) | 13 (34) | 17 (40) | 42 (35) |
| ECOG PS (0/1/2), n (%) | 7/27/6 (18/68/15) | 9/23/6 (24/61/16) | 8/27/8 (19/63/19) | 24/77/20 (20/64/17) |
| Number of brain metastases, n (%) | | | | |
| ≤3 | 17 (43) | 15 (40) | 18 (42) | 50 (41) |
| >3 | 23 (58) | 23 (61) | 25 (58) | 71 (59) |
| Positive hormone receptor status, n (%) | 25 (63) | 16 (42) | 18 (42) | 59 (49) |
| Number of metastatic sites, n (%) | | | | |
| ≤3 | 32 (80) | 31 (82) | 31 (72) | 94 (78) |

| | | | | |
|---|---|---|---|---|
| >3 | 8 (20) | 7 (18) | 11 (26) | 26 (22) |
| Not available | 0 | 0 | 1 (2) | 1 (1) |
| Liver involvement, n (%) | 14 (35) | 10 (26) | 19 (44) | 43 (36) |
| Prior chemotherapy, n (%) | | | | |
| None | 0 | 0 | 1 (2) | 1 (1) |
| 1–2 regimens | 10 (25) | 12 (32) | 15 (35) | 37 (31) |
| >2 regimens | 30 (75) | 26 (68) | 26 (61) | 82 (68) |
| Unavailable | 0 | 0 | 1 (2) | 1 (1) |
| Prior brain radiotherapy, n (%) | 34 (85) | 30 (79) | 37 (86) | 101 (84) |
| No WBRT and no SRT | 7 (18) | 2 (5) | 8 (19) | 17 (14) |
| No WBRT but SRT | 1 (3) | 0 | 3 (7) | 4 (3) |
| WBRT and no SRT | 24 (60) | 25 (66) | 25 (58) | 74 (61) |
| WBRT and SRT | 2 (5) | 3 (8) | 1 (2) | 6 (5) |
| Prior trastuzumab, n (%) | 40 (100) | 38 (100) | 43 (100) | 121 (100) |
| As neoadjuvant therapy | 8 (20) | 6 (16) | 8 (19) | 22 (18) |
| As adjuvant therapy† | 12 (30) | 15 (40) | 20 (47) | 47 (39) |
| In advanced/palliative setting | 30 (75) | 30 (79) | 36 (84) | 96 (79) |
| Prior lapatinib, n (%)‡ | 32 (80) | 30 (79) | 33 (77) | 95 (79) |
| As adjuvant therapy | 1 (3) | 2 (5) | 4 (9) | 7 (6) |
| In advanced/palliative setting | 30 (75) | 28 (74) | 28 (65) | 86 (71) |

ECOG PS=Eastern Cooperative Oncology Group performance score. IQR=interquartile range. SRT=stereotactic radiation therapy. WBRT=whole brain radiotherapy. *Routine collection of race is forbidden in France. †Neoadjuvant treatment with trastuzumab or lapatinib, with continuation in the adjuvant setting for a total of no more than one year, was considered adjuvant. ‡Prior lapatinib was a stratification

factor and included adjuvant or metastatic treatment; mode of lapatinib therapy was missing in 4 patients, and some patients received lapatinib in the adjuvant and advanced/palliative setting.

***Table 2*: Patient benefit, survival outcomes and anti-tumour activity in the three study groups**

| | **Group A (afatinib monotherapy) n=40** | **Group B (afatinib and vinorelbine) n=38** | **Group C (investigator's choice) n=43** |
|---|---|---|---|
| Patient benefit at 12 weeks, n (%) | 12 (30) | 13 (34) | 18 (42) |
| (95% CI) | (16·6–46·5) | (19·6–51·4) | (27·0–57·9) |
| Difference versus group C (95% CI) | –11.9 (–32.9 to 9.7) | –7.6 (–28.9 to 14.2) | |
| p value | 0·37 | 0·63 | |
| Progression-free survival (weeks) | | | |
| Median | 11·9 | 12·3 | 18·4 |
| (IQR) | (6·1–20·9) | (6·3–23·3) | (8·3–30·7) |
| HR* (*vs* group C) | 1·18 | 0·94 | |
| 95% CI for HR* | (0·72–1·93) | (0·57–1·54) | |
| p value | 0·51 | 0·78 | |
| Overall survival (weeks) | | | |
| Median | 57·7 | 37·3 | 52·1 |
| (IQR) | (34·1–81·3) | (21·0–66·7) | (29·1–122·6) |
| HR* (*vs* group C) | 1·27 | 1·60 | |
| 95% CI for HR* | (0·72–2·21) | (0·93–2·76) | |
| p value | 0·41 | 0·09 | |
| Objective response rate†, n (%) | | | |
| CNS lesions‡ | 0 | 3 (8) | 6 (14) |

| | | | |
|---|---|---|---|
| Median (range) duration of response, days | NA | 46 (13–70) | 192 (94–743) |
| Extra-CNS lesions§ | 0 | 3 (8) | 2 (5) |
| Median (range) duration of response, days | NA | 192 (108–235) | 170 (108–232) |
| Disease control¶, n (%) | | | |
| CNS lesions‡ | 27 (68) | 27 (71) | 31 (72) |
| Extra-CNS lesions§ | 17 (43) | 19 (50) | 26 (61) |

CI=confidence interval. CNS=central nervous system. ECOG PS=Eastern Cooperative Oncology Group performance score. HR=hazard ratio. IQR=interquartile range. NA = not applicable. *From Cox proportional−hazards regression model, stratified by ECOG PS at baseline (0−1 *vs* 2), number of brain metastases at screening (≤3 *vs* >3), and prior treatment with lapatinib (yes *vs* no). †Complete or partial response. ‡Tumour response was not assessed in groups A, B, and C for 4, 4, and 5 patients, respectively. §Tumour response was not assessed in groups A, B, and C for 13, 16, and 13 patients, respectively. ¶Complete response, partial response, or stable disease for ≥6 weeks.

***Table 3.*** **Progression by tumour site (CNS lesions, extra-CNS lesions or both)**

| | **Group A (afatinib monotherapy) N=40)** | **Group B (afatinib and vinorelbine) n=38** | **Group C (investigator's choice) n=43** |
|---|---|---|---|
| Progression by RECIST v1.1 during the trial, n (%) | 31 (78) | 24 (63) | 30 (70) |
| Progression in CNS and extra-CNS lesions, n (%) | 5 (13) | 4 (11) | 5 (12) |
| Progression in CNS lesions only, n (%) | 19 (48) | 16 (42) | 19 (44) |
| Patients with extra-CNS lesions | 12 (30) | 8 (21) | 14 (33) |
| Patients without extra-CNS lesions | 7 (18) | 8 (21) | 5 (12) |
| Progression in extra-CNS lesions only, n (%) | 7 (18) | 4 (11) | 6 (14) |
| No progression by RECIST v1.1 during the trial, n (%) | 9 (23) | 14 (37) | 13 (30) |
| Patients with extra-CNS lesions | 7 (18) | 10 (26) | 8 (19) |
| Patients without extra-CNS lesions | 2 (5) | 4 (11) | 5 (12) |

***Table 4*: Most common treatment-related AEs**

| | **Group A (afatinib monotherapy) n=40** | | | **Group B (afatinib and vinorelbine) n=37** | | | **Group C (investigator's choice) n=42** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **G1–2** | **G3** | **G4** | **G1–2** | **G3** | **G4** | **G1–2** | **G3** | **G4** |
| Any drug-related AE | 18 (45) | 20 (50) | 1 (3) | 5 (14) | 21 (57) | 9 (24) | 18 (43) | 6 (14) | 3 (7) |
| Neutropenia | 0 | 0 | 0 | 5 (14) | 10 (27) | 4 (11) | 5 (12) | 2 (5) | 2 (5) |
| Diarrhoea | 29 (73) | 7 (18) | 0 | 22 (59) | 9 (24) | 0 | 12 (29) | 2 (5) | 0 |
| Mucosal inflammation | 6 (15) | 1 (3) | 1 (3) | 9 (24) | 3 (8) | 0 | 6 (14) | 0 | 0 |
| Stomatitis | 3 (8) | 3 (8) | 0 | 8 (22) | 3 (8) | 0 | 4 (10) | 0 | 0 |
| Asthenia | 6 (15) | 4 (10) | 0 | 6 (16) | 3 (8) | 0 | 7 (17) | 2 (5) | 0 |
| Rash | 14 (35) | 0 | 1 (3) | 18 (49) | 2 (5) | 0 | 3 (7) | 0 | 0 |
| Anaemia | 0 | 0 | 0 | 7 (19) | 2 (5) | 0 | 2 (5) | 0 | 0 |
| Vomiting | 4 (10) | 1 (3) | 0 | 6 (16) | 1 (3) | 0 | 5 (12) | 0 | 0 |
| Fatigue | 2 (5) | 0 | 0 | 4 (11) | 1 (3) | 0 | 2 (5) | 0 | 0 |
| Leukopenia | 0 | 0 | 0 | 1 (3) | 1 (3) | 1 (3) | 2 (5) | 2 (5) | 0 |
| Febrile neutropenia | 0 | 0 | 0 | 0 | 1 (3) | 1 (3) | 0 | 0 | 1 (2) |
| Nausea | 8 (20) | 0 | 0 | 11 (30) | 0 | 0 | 7 (17) | 0 | 0 |
| Paronychia | 3 (8) | 2 (5) | 0 | 6 (16) | 0 | 0 | 1 (2) | 0 | 0 |
| Epistaxis | 4 (10) | 0 | 0 | 5 (14) | 0 | 0 | 0 | 0 | 0 |
| Dry skin | 7 (18) | 0 | 0 | 4 (11) | 0 | 0 | 0 | 0 | 0 |
| Decreased appetite | 6 (15) | 2 (5) | 0 | 3 (8) | 0 | 0 | 6 (14) | 0 | 0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Constipation | 2 (5) | 0 | 0 | 3 (8) | 0 | 0 | 7 (17) | 0 | 0 |
| Alopecia | 0 | 0 | 0 | 1 (3) | 0 | 0 | 8 (19) | 0 | 0 |
| Dermatitis acneiform | 4 (10) | 3 (8) | 0 | 1 (3) | 0 | 0 | 0 | 0 | 0 |
| Myalgia | 1 (3) | 0 | 0 | 1 (3) | 0 | 0 | 4 (10) | 0 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | 6 (15) | 0 | 0 | 0 | 0 | 0 | 4 (10) | 0 | 0 |
| Neuropathy peripheral | 0 | 0 | 0 | 0 | 0 | 0 | 4 (10) | 0 | 0 |

Data are n (%). Events are included in the table if reported for at least 10% of patients (grades 1–2) in any treatment group or any grade 3 or 4 event reported in more than one patient.*No treatment-related grade 5 events were reported; AE=adverse event. G=grade.

Additional grade 3–4 AEs reported in the afatinib monotherapy group that are not shown in the table were: conjuctivitis (one [3%]); skin lesion (one [3%]), generalised rash (one [3%]), acute renal failure (one [3%]), general physical health deterioration (one [3%]); additional grade 3–4 AEs reported in the afatinib plus vinorelbine group were: lung infection (one [3%]), urosepsis (one [3%]), lymphopenia (one [3%]), febrile bone marrow aplasia (one [3%]), hypokalaemia (one [3%]), dizziness (one [3%]), partial seizures (one [3%]), dysphagia (one [3%]), enteritis (one [3%]), dermatitis (one [3%]), skin ulcer (one [3%]), elevated serum alanine aminotransferase (one [3%]), low blood lymphocyte count (one [3%]) and low blood neutrophil count (one [3%]); additional grade 3–4 AEs reported in the investigator's choice group were: low white blood cell count (one [2%]) and abdominal pain (one [2%])

***Figure 1*: Patient disposition**

*Two patients were randomised in error and were not treated: one patient in the investigator's choice arm, and one patient in the combination therapy arm.

***Figure 2*: PFS (A) and OS (B) for each study group (afatinib monotherapy, afatinib and vinorelbine, and investigator's choice)**

CI=confidence interval. OS=overall survival. PFS=progression-free survival.

***Figure 3*: Waterfall plot of maximum decrease from baseline in the sum of longest diameters of CNS target lesions**

CNS=central nervous system.