Afatinib alone or afatinib plus vinorelbine versus investigator's choice of treatment for HER2-positive breast cancer with progressive brain metastases after trastuzumab, lapatinib, or both (LUX-Breast 3): a randomised, open-label, multicentre, phase 2 trial

Javier Cortés, Véronique Dieras, Jungsil Ro, Jérôme Barriere, Thomas Bachelot, Sara Hurvitz, Emilie Le Rhun, Marc Espié, Sung-Bae Kim, Andreas Schneeweiss, Joo Hyuk Sohn, Jean-Marc Nabholtz, Pirkko-Liisa Kellokumpu-Lehtinen, Julie Taguchi, Federico Piacentini, Eva Ciruelos, Petri Bono, Mahmoud Ould-Kaci, Flavien Roux, Heikki Joensuu

Lancet Oncol 2015; 16: 1700–10

Published Online November 16, 2015 http://dx.doi.org/10.1016/S1470-2045(15)00373-3

See Comment page 1583

Vall d'Hebron Institute of Oncology, Barcelona, Spain and Ramon y Cajal University Hospital, Madrid, Spain (J Cortés MD); **Institut Curie, Paris, France** (V Dieras MD); **National Cancer Center, Goyang-si, Republic of Korea** (J Ro MD); **Centre Antoine Lacassagne, Nice, France** (J Barriere MD); **Centre Léon Bérard, Lyon, France** (T Bachelot MD); **University of California, Los Angeles, CA, USA** (S Hurvitz MD); **Centre Oscar Lambret, Lille, France, and University Hospital, Lille, France** (E Le Rhun MD); **Hôpital Saint-Louis, Paris, France** (M Espié MD); **Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea** (S-B Kim MD); **National Center for Tumor Diseases, University Hospital, Heidelberg, Germany** (A Schneeweiss MD); **Severance Hospital, Sinchon-dong, Seodaemun-gu, Seoul, South Korea** (J H Sohn MD); **Centre Jean Perrin, Clermont-Ferrand, France** (Prof J-M Nabholtz MD); **Tampere University Hospital and University of Tampere, Tampere, Finland** (Prof P-L Kellokumpu-Lehtinen MD); **Sansum Clinic, Santa Barbara, CA, USA** (J Taguchi MD); **Università di Modena e Reggio Emilia, Modena, Italy** (F Piacentini MD); **Hospital Universitario 12 de Octubre, Madrid, Spain** (E Ciruelos MD); **Comprehensive Cancer Center, Helsinki University Hospital, and University of Helsinki,**

Summary

Background Patients with advanced HER2-positive breast cancer frequently develop CNS metastases. The metastases that progress after brain radiotherapy and HER2-targeted systemic therapy are a difficult therapeutic challenge. We aimed to assess the efficacy and safety of afatinib, an irreversible blocker of the ErbB protein family, alone or combined with vinorelbine, compared with treatment of the investigator's choice in women with HER2-positive breast cancer with progressive brain metastases during or after treatment with trastuzumab, lapatinib, or both.

Methods We did this randomised, open-label, multicentre, phase 2 trial in 40 hospitals in Canada, Finland, France, Germany, Italy, Spain, South Korea, and the USA. Women older than 18 years with histologically confirmed HER2-overexpressing breast cancer and CNS recurrence or progression as determined by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) during or after treatment with trastuzumab, lapatinib, or both, were eligible. We randomly assigned patients (1:1:1) centrally to afatinib 40 mg orally once per day, afatinib 40 mg per day plus intravenous vinorelbine 25 mg/m^2 once per week, or investigator's choice of treatment in cycles of 3 weeks until disease progression, patient withdrawal, or unacceptable toxicity. Treatment assignment was not masked for clinicians or patients, but the trial team was masked until database lock to reduce bias. The primary endpoint, assessed in the intention-to-treat population, was patient benefit at 12 weeks, defined by an absence of CNS or extra-CNS disease progression, no tumour-related worsening of neurological signs or symptoms, and no increase in corticosteroid dose. Safety was assessed in all patients who received at least one dose of a study drug. This completed trial is registered with ClinicalTrials.gov, number NCT01441596.

Findings Between Dec 22, 2011, and Feb 12, 2013, we screened 132 patients, of whom 121 were eligible and randomly assigned to treatment: 40 to afatinib alone, 38 to afatinib plus vinorelbine, and 43 to investigator's choice. All patients discontinued study treatment before the data collection cutoff on Oct 16, 2014. Patient benefit was achieved in 12 (30·0%; 95% CI 16·6–46·5) patients given afatinib alone (difference *vs* investigator's choice: –11·9% [95% CI –32·9 to 9·7], p=0·37), 13 (34·2%; 19·6–51·4) given afatinib plus vinorelbine (difference *vs* investigator's choice: –7·6% [–28·9 to 14·2], p=0·63), and 18 (41·9%; 27·0–57·9) given investigator's choice. The most common treatment-related grade 3 or 4 adverse events were diarrhoea (seven [18%] of 40 patients in the afatinib only group *vs* nine [24%] of 37 patients in the afatinib plus vinorelbine group *vs* two [5%] of 42 patients in the investigator's choice group) and neutropenia (none *vs* 14 [38%] *vs* four [10%]).

Interpretation Patient benefit with afatinib-containing treatments was not different from that in patients given investigator's choice of treatments; however, adverse events were frequent and afatinib-containing treatments seemed to be less well tolerated. No further development of afatinib for HER2-positive breast cancer is currently planned.

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 patients with breast cancer and brain metastases are still short—about 2 years after the first detection of metastatic lesions.[2–4] Local therapies, including whole-brain irradiation or stereotactic radiation therapy, surgery, and combinations of these treatments, are the standard of care for brain metastases. No systemic

Research in context

Evidence before this study

We did a systematic review of the scientific literature published up to March 31, 2015, using PubMed. Using the search terms "brain metastases", "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 identified a high unmet need for effective treatment in patients with brain metastases previously given radiotherapy that had progressed during HER2-targeted treatment. No systemic therapies have been specifically approved for the treatment of breast cancer brain metastases.

Added value of this study

To our knowledge, this study is the first randomised trial to compare afatinib alone or afatinib plus vinorelbine with investigator's choice of treatment in patients with HER2-positive breast cancer with progressive brain metastases after previous treatment with trastuzumab, lapatinib, or both. We showed that about one-third of patients with HER2-positive metastatic breast cancer probably benefited from their assigned treatments, based on predefined criteria; however, the regimens containing afatinib did not have better activity than investigator-selected treatments, which usually consisted of trastuzumab or lapatinib combined with chemotherapy. Afatinib-containing regimens also seemed to be less well tolerated than the investigator's choice regimens.

Implications of all the available evidence

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

Helsinki, Finland (P Bono MD, Prof H Joensuu MD); **Boehringer Ingelheim, Paris, France** (M Ould-Kaci MD); **Boehringer Ingelheim, Reims, France** (F Roux MSc)

Correspondence to:
Dr Javier Cortés, Vall d'Hebron Institute of Oncology, Psg. Vall d'Hebron 119-129, 08035 Barcelona, Spain
jacortes@vhio.net

therapies are specifically approved for the treatment of patients with breast cancer and brain metastases.[1] However, in a phase 2 trial[5] the HER2/EGFR tyrosine kinase inhibitor lapatinib, in combination with capecitabine, showed substantial activity in patients with HER2-positive breast cancer who had brain metastases but had not received whole-brain radiotherapy. An objective response was achieved in 29 (66%) of 44 patients; however, 22 (49%) of 45 treated patients had grade 3 or 4 treatment-related adverse events.

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

Afatinib is an oral, irreversible inhibitor of the ErbB family of proteins.[8] In a phase 2 trial,[9] afatinib showed activity in patients with metastatic HER2-positive breast cancer who were previously given trastuzumab and chemotherapy. In preclinical studies,[10] the antitumour activity of afatinib was increased by adding vinorelbine. This combination also showed activity in phase 1 trials in patients with advanced solid tumours,[10,11] and was thus taken forward for investigation in phase 3 trials. 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, these clinical data suggest that afatinib could traverse the blood–brain barrier sufficiently to elicit antitumour activity in patients with breast cancer brain metastases. Furthermore, because afatinib, unlike lapatinib and trastuzumab, is an irreversible inhibitor of HER2,[14] we postulated that afatinib might be effective in patients with brain metastases that had progressed during treatment with these drugs. In this hypothesis-generating, randomised study, we treated women with HER2-positive breast cancer with brain metastases that progressed during or after treatment with trastuzumab, lapatinib, or both, with afatinib monotherapy, afatinib plus vinorelbine, or a treatment of investigator's choice.

Methods

Study design and patients

This randomised, open-label, multicentre, phase 2 trial was done at 40 centres (that were both cancer centres and hospitals) in Canada, Finland, France, Germany, Italy, Spain, South Korea, and the USA (appendix). The protocol was approved by local institutional review boards or ethics committees in each country that the study took place in, and the study was done in compliance with the International Conference on Harmonization Good Clinical Practice and the declaration of Helsinki.

See Online for appendix

Eligible patients were women aged 18 years or older with histologically confirmed HER2-overexpressing breast cancer as per local assessment, with CNS recurrence or progression as measured by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 during or after treatment with trastuzumab, lapatinib, or both. Other inclusion criteria included the presence of at least one measurable and progressive lesion in the CNS (≥10 mm on T1-weighted, gadolinium-enhanced MRI) after previous systemic therapy, radiation therapy, or

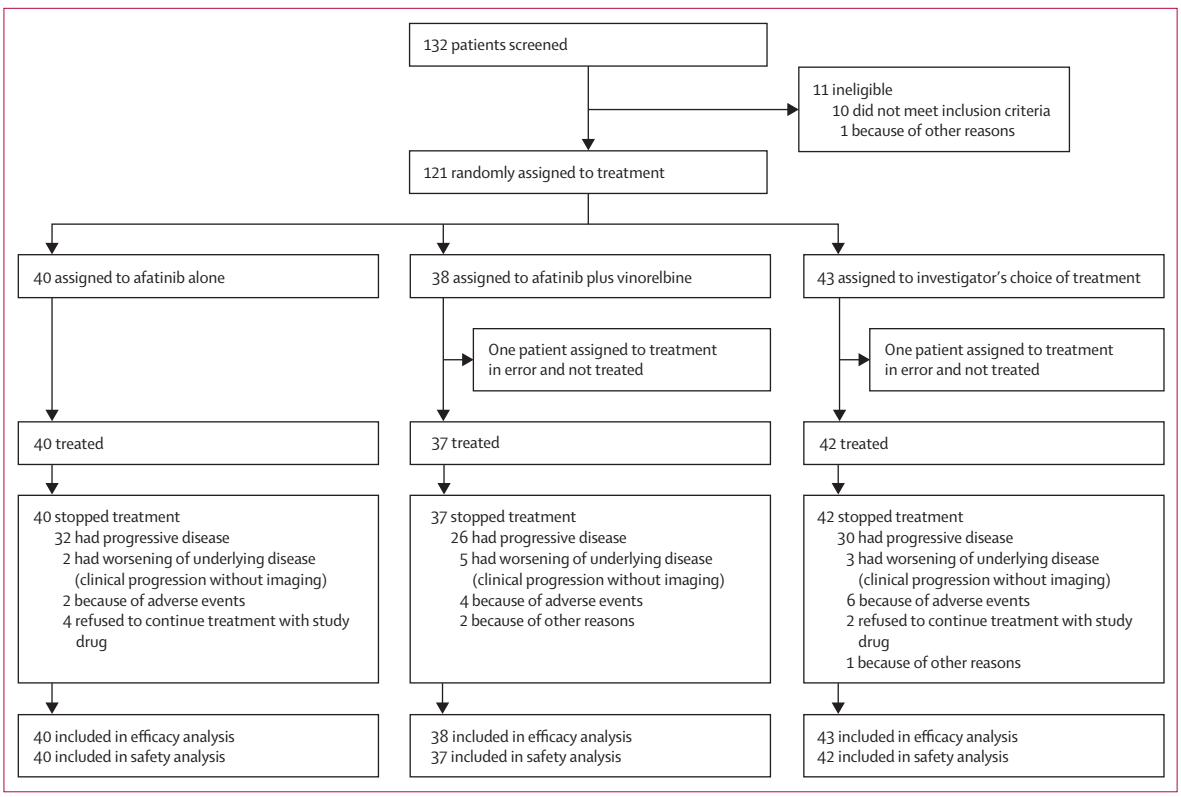

***Figure 1*: Trial profile**

both; an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2; and a life expectancy of at least 3 months. Key exclusion criteria were previous treatment with a HER2-tyrosine kinase inhibitor other than lapatinib; HER2-inhibitor treatment within 14 days (trastuzumab or other antibodies) or 7 days (lapatinib) of study start; having had surgery within 4 weeks, radiotherapy, stereotactic radiosurgery, chemotherapy, or investigational therapy within 14 days, or hormonal therapy within 7 days before study start; pre-existing interstitial lung disease, leptomeningeal carcinomatosis as the only site of CNS metastases, and having substantial gastrointestinal disorders with diarrhoea as a major symptom. Additionally, patients were excluded if they had an absolute blood neutrophil count of fewer than $1{\cdot}5\times10^9$ cells per L, a platelet count of fewer than 100×10^9 cells per L, a calculated serum creatinine clearance less than 60 mL/min or a serum creatinine concentration greater than 1·5×the upper limit of normal (ULN), a bilirubin concentration greater than 1·5×ULN, or aspartate aminotransferase or alanine aminotransferase concentrations greater than 3×ULN (or if related to liver metastases, >5×ULN). Patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1:1) at Perceptive Informatics (Nottingham, UK), a company outsourced by Boehringer Ingelheim, to afatinib, afatinib plus vinorelbine, or investigator's choice of treatment, which could include any chemotherapy or medical treatment approved for advanced or metastatic breast cancer. Randomisation was stratified according to the ECOG performance score (0–1 *vs* 2), the number of brain metastases at screening (≤three *vs* >three), and previous treatment with lapatinib (yes *vs* no). The randomisation used block sizes of six and the randomisation was done with a validated random number generator implemented with an interactive voice or web response system.

Treatment assignment was not masked for clinicians, or patients because of the different treatment schedules in each group. To reduce bias, the Boehringer Ingelheim trial team (MO-K and FR) was masked to treatment allocation and results until the first main analysis in March, 2014. After this time, the trial team was unmasked.

Procedures

For patients receiving afatinib alone, the initial dose was 40 mg once per day (the standard dose for phase 3 trials), which could be increased to 50 mg per day from cycle 2 if the patient did not have diarrhoea, skin-related adverse events, mucositis, or any drug-related adverse event that was grade 2 or worse. If patients had any drug-related adverse events of grade 3 or worse, grade 2 diarrhoea lasting 2 or more days, nausea or vomiting for 7 or more

consecutive days despite best supportive care, or decreased renal function of grade 2 or worse, then afatinib was paused for up to 14 days until recovery to grade 1 or 0 or to baseline values. Afatinib was then resumed at a lower dose (10 mg decrements to a minimum dose of 20 mg per day). If the patient did not recover to baseline or grade 1 or less of Common Terminology Criteria for Adverse Events within 14 days, afatinib was permanently discontinued. Additional criteria for removal of individual patients included patient withdrawal of consent, documented progressive disease, or that the patient was no longer able to receive any of the study treatments because of pregnancy, concomitant diagnoses, etc. Patients in the afatinib plus vinorelbine group received afatinib 40 mg once per day plus vinorelbine 25 mg/m² given as one intravenous infusion per week (no patients in this group were allowed to be given 50 mg afatinib, according to the trial protocol). Afatinib dose reductions were done if adverse events occurred (as detailed for the afatinib alone group) and vinorelbine doses could be skipped in case of tolerability issues in accordance with the product information (vinorelbine dose reductions to 20 mg/m² each week were allowed if deemed necessary by the investigator and the patient was deriving clinical benefit). Patients could discontinue vinorelbine under the same circumstances as for afatinib.

For the investigator's choice group, treatment comprised any chemotherapy or medical treatment approved for advanced or metastatic breast cancer (however, best supportive care alone was not allowed). Treatments were given in accordance with product information or local treatment guidelines, thus dose reductions were not expected for these drugs. For all three study groups, concomitant drugs could be given as clinically needed (eg, corticosteroids, bisphosphonates, anticonvulsants, and growth factor support), and palliative radiotherapy for non-target lesions was allowed because of the late-stage setting of this trial.

We gave all assigned study treatments in 3-week cycles until disease progression (CNS or extra-CNS lesions), occurrence of unacceptable adverse events, or withdrawal of consent; for reasons of practicality, study treatment was divided into courses of 3 weeks (21 days) duration. We assessed tumours with gadolinium-enhanced MRI of the brain and CT of the chest and abdomen at screening, every 6 weeks for the first 12 weeks, then every 9 weeks until disease progression, death, or last follow-up. Neurological symptoms were assessed by the investigator using the Neurological Examination Worksheet at screening and at each tumour assessment. We deemed a decline of two or more Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 levels for at least 7 days for a neurological sign or symptom as neurological deterioration, unless it was attributable to comorbid events or changes in corticosteroid dose. We graded adverse events according to CTCAE version 3.0. We followed patients for safety 28 days after discontinuing study therapy and every 6 to 9 weeks thereafter until disease progression or start of further treatment. We then followed patients every 60 days, by patient records, telephone, or visits, until death or end of trial.

	Afatinib alone n=40	Afatinib plus vinorelbine n=38	Investigator's choice n=43
Age (years)	53 (43–58)	53 (44–57)	51 (44–63)
Post-menopausal	28 (70%)	29 (76%)	31 (72%)
Ethnic origin			
White	21 (53%)	19 (50%)	20 (47%)
Asian	6 (15%)	6 (16%)	6 (14%)
Black or African-American	1 (3%)	0	0
Not recorded*	12 (30%)	13 (34%)	17 (40%)
ECOG performance score			
0	7 (18%)	9 (24%)	8 (19%)
1	27 (68%)	23 (61%)	27 (63%)
2	6 (15%)	6 (16%)	8 (19%)
Number of brain metastases			
≤3	17 (43%)	15 (39%)	18 (42%)
>3	23 (58%)	23 (61%)	25 (58%)
Hormone receptor positive	25 (63%)	16 (42%)	18 (42%)
Number of metastatic sites			
≤3	32 (80%)	31 (82%)	31 (72%)
>3	8 (20%)	7 (18%)	11 (26%)
Information not available	0	0	1 (2%)
Liver metastases	14 (35%)	10 (26%)	19 (44%)
Previous chemotherapy			
None	0	0	1 (2%)
1–2 regimens	10 (25%)	12 (32%)	15 (35%)
>2 regimens	30 (75%)	26 (68%)	26 (60%)
Information not available	0	0	1 (2%)
Previous brain radiotherapy	34 (85%)	30 (79%)	37 (86%)
No WBRT and no SRT	7 (18%)	2 (5%)	8 (19%)
SRT but no WBRT	1 (3%)	0 (0%)	3 (7%)
WBRT but no SRT	24 (60%)	25 (66%)	25 (58%)
Both WBRT and SRT	2 (5%)	3 (8%)	1 (2%)
Previous trastuzumab	40 (100%)	38 (100%)	43 (100%)
As neoadjuvant therapy	8 (20%)	6 (16%)	8 (19%)
As adjuvant therapy†	12 (30%)	15 (39%)	20 (47%)
In advanced or palliative settings	30 (75%)	30 (79%)	36 (84%)
Previous lapatinib‡	32 (80%)	30 (79%)	33 (77%)
As adjuvant therapy	1 (3%)	2 (5%)	4 (9%)
In advanced or palliative settings	30 (75%)	28 (74%)	28 (65%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. SRT=stereotactic radiation therapy. WBRT=whole brain radiotherapy. *Obtaining data about race is not routinely allowed in France. Because no justification could be provided, data about race were not obtained for this trial. †Neoadjuvant treatment with trastuzumab or lapatinib, with continuation in the adjuvant setting for a total of no more than 1 year, was deemed adjuvant. ‡Previous lapatinib was a stratification factor and included adjuvant or metastatic treatment; details about the method of lapatinib therapy were missing for four patients, and some patients received lapatinib in both the adjuvant and advanced or palliative settings.

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

Outcomes

The primary endpoint, assessed by the investigator, was patient benefit at 12 weeks after the date of randomisation

	Afatinib alone n=40	Afatinib plus vinorelbine n=38	Investigator's choice n=43
Patient benefit at 12 weeks (primary outcome)			
Number of patients	12 (30·0%; 16·6–46·5)	13 (34·2%; 19·6–51·4)	18 (41·9%; 27·0–57·9)
Difference (95% CI) versus investigator's choice group, p value	−11·9 (−32·9 to 9·7), 0·37	−7·6 (−28·9 to 14·2), 0·63	..
Progression-free survival			
Duration (weeks)	11·9 (6·3–18·7)	12·3 (7·4–17·3)	18·4 (11·1–21·1)
HR (95% CI)* versus investigator's choice group , p value	1·18 (0·72–1·93), 0·51	0·94 (0·57–1·54), 0·78	..
Overall survival			
Duration (weeks)	57·7 (39·3–68·1)	37·3 (25·3–57·3)	52·1 (39·3–80·4)
HR (95% CI)* versus investigator's choice group, p value	1·27 (0·72–2·21), 0·41	1·60 (0·93–2·76), 0·09	..
Proportion of patients with an objective response†			
CNS lesions‡	0	3 (8%)	6 (14%)
Median (IQR) duration of response (days)	..	46 (13–70)	192 (135–247)
Extra-CNS lesions§	0	3 (8%)	2 (5%)
Median (IQR) duration of response (days)	..	192 (108–235)	170 (108–232)
Disease control¶			
CNS lesions‡	27 (68%)	27 (71%)	31 (72%)
Extra-CNS lesions§	17 (43%)	19 (50%)	26 (61%)

Data are n (%; 95% CI), n (%), or median (95% CI) unless otherwise stated. ..=not applicable. HR=hazard ratio. *From Cox proportional hazards regression model, stratified by Eastern Cooperative Oncology Group performance score at baseline, number of brain metastases at screening, and previous treatment with lapatinib. †Complete or partial response. ‡Tumour response was not assessed in four patients in the afatinib alone group, four patients in the afatinib plus vinorelbine group, and five patients in the investigator's choice group. ¶Complete response, partial response, or stable disease for at least 6 weeks. §Tumour response was not assessed in 13 patients in the afatinib group, 16 patients in the afatinib plus vinorelbine group, and 13 patients in the investigator's choice group.

***Table 2*: Patient benefit, survival outcomes, and tumour response**

on the basis of the following criteria, each of which had to be met: absence of CNS disease progression according to RECIST version 1.1, no tumour-related worsening of neurological signs or symptoms, no increase in corticosteroid dose, and no progression of extra-CNS disease.

Secondary endpoints were progression-free survival (the time from randomisation to disease progression in either CNS or extra-CNS lesions, or death, whichever happened first), and overall survival (the time from randomisation to death from any cause). Other endpoints included the proportion of patients who achieved an objective response with CNS and extra-CNS lesions (the best overall response assessed by investigators according to RECIST version 1.1), disease control (complete response, partial response, or stable disease for ≥6 weeks), and safety. We calculated the duration of response from the date of the first documented complete response or partial response to the date of progression or death, whichever happened first.

Statistical analysis

This was an exploratory trial and, as such, we did not do a formal sample size calculation. However, we assumed that the proportion of patients having a clinical benefit would be 35% for patients given afatinib alone, 40% for afatinib plus vinorelbine, and 25% for investigator's choice, and calculated that a sample size of 40 patients per group would be needed for an 80% probability of correctly preferring afatinib alone versus investigator's choice, and a 90% probability of correctly preferring afatinib plus vinorelbine versus investigator's choice, using Simon's selection criteria.[15]

We did the efficacy analyses in the intention-to-treat (ITT) population including all randomly assigned patients. For the analysis of patient benefit, we calculated Clopper-Pearson 95% CIs for the proportion of patients with clinical benefit in each study group, and for between-group differences (afatinib alone or afatinib plus vinorelbine *vs* investigator's choice). We compared differences between groups using the Wald asymptotic test with a continuity correction. We analysed survival with the Kaplan-Meier life-table method. We compared survival between groups with the likelihood score test and calculated hazard ratios (HRs) using a univariate Cox model, and Greenwood's variance estimate used to establish CIs. We used the Wald test to verify that the proportionality assumption was valid. In view of the exploratory nature of these analyses, all reported CIs and p values should be regarded with caution. The safety population comprised all patients receiving one or more doses of study drug.

We did the statistical analyses with SAS (version 9.2). A benefit-risk analysis was done by the independent data monitoring committee team when 20 patients had been treated in each treatment group to identify whether to proceed with the trial or stop one of the treatment groups for futility (appendix). The study is registered with ClinicalTrials.gov, number NCT01441596.

Role of the funding source

The funder of the study provided most of the study drugs (for investigator's choice of treatment, drugs were provided by the funder in some countries, and in some other countries commercial drugs were used), and had a role in study design in collaboration with HJ, data collection through management of the clinical trial database, and data analysis, and financially supported medical writers who assisted with writing the report. HJ had full access to the study data. All authors, in collaboration with the funder, interpreted the data and were involved in manuscript development. All authors approved the final version of the manuscript and made the final decision to submit the report for publication.

Results

Between Dec 22, 2011, and Feb 12, 2013, we screened 132 patients and randomly assigned 121 to treatment; 119 received the study drug (figure 1). Demographics and baseline characteristics were generally well balanced across the groups (table 1). All patients discontinued study treatment before data collection cutoff on Oct 16, 2014 (figure 1). No patients had palliative radiotherapy before disease progression during the trial.

Median duration of treatment was 10·2 weeks (IQR 6·0–17·3) for afatinib alone, 11·4 weeks (6·1–21·0) for afatinib plus vinorelbine, and 12·6 weeks (5·1–21·9) for investigator's choice; the median number of treatment courses completed were 3·5 (IQR 2·0–6·0), 4·0 (2·0–6·0), and 4·0 (2·0–7·0), respectively. In all three groups, disease progression, which was confirmed by CT scan, MRI, or both, was the most common reason for stopping treatment (figure 1), except in 10 cases (detected clinically without imaging). Treatments given in the investigator's choice group were trastuzumab plus chemotherapy (22 [52%] of 42 patients, of whom 11 [50%] received trastuzumab plus vinorelbine); trastuzumab plus lapatinib plus chemotherapy (three patients [7%]); lapatinib plus chemotherapy (10 patients [24%]); lapatinib alone (one patient [2%]), or chemotherapy alone (six patients [14%]; appendix). Median times from the first drug intake to the last were 71·5 (IQR 42·0–121·0) for afatinib alone, 80·0 (43·0–147·0) for afatinib plus vinorelbine, 88·0 (36·0–153·0) for investigator's choice, and 80·0 (42·0–147·0) for all groups combined.

Patient benefit at 12 weeks was achieved in 12 (30·0%; 95% CI 16·6–46·5) of 40 patients given afatinib alone, 13 (34·2%; 19·6–51·4) of 38 patients given afatinib plus vinorelbine, and 18 (41·9%; 27·0–57·9) of 43 patients given investigator's choice (table 2).

Data for neurological signs and symptoms (as assessed by the Neurological Examination worksheet) and changes in patients' corticosteroid doses are in the appendix. There was no difference in median progression-free survival or in median overall survival between the treatment groups (table 2; figure 2). The proportionality assumptions of the Cox models used to calculate the HRs were valid (for progression-free survival p=0·70; for overall survival p=0·22). Disease progression by tumour site is shown in table 3.

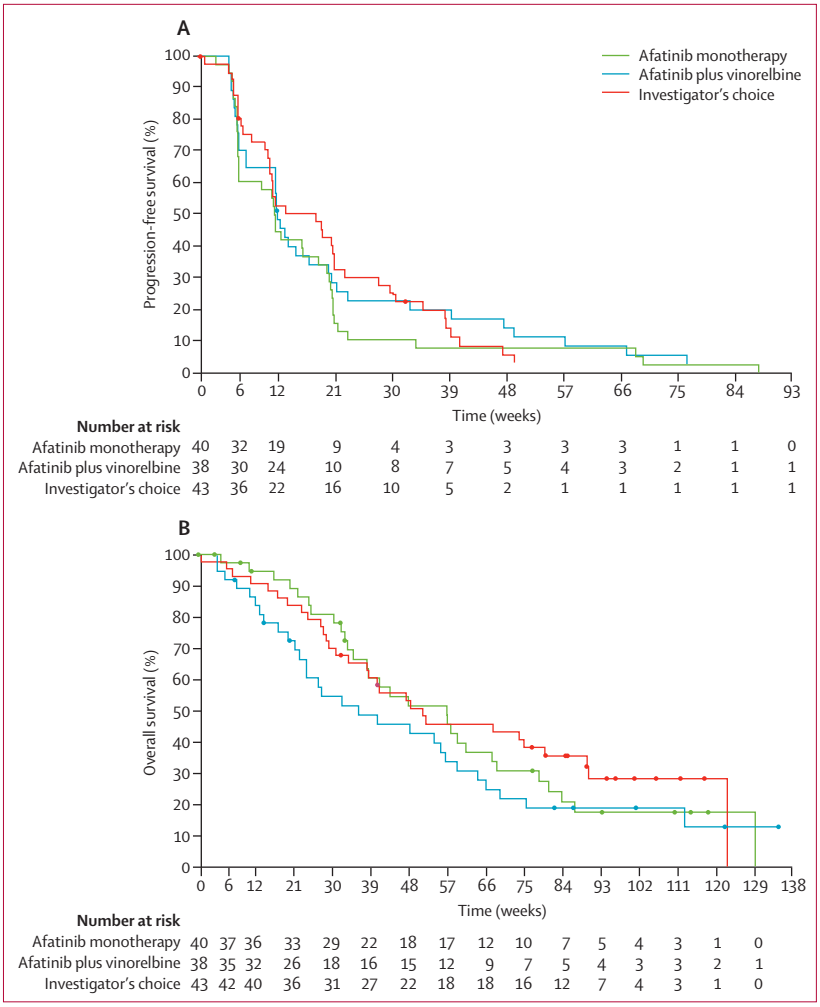

Figure 2: **Kaplan-Meier plot for progression-free survival (A) and overall survival (B)**

	Afatinib alone N=40	Afatinib plus vinorelbine n=38	Investigator's choice n=43
Progression during the trial*	31 (78%)	24 (63%)	30 (70%)
Progression in CNS and extra-CNS lesions	5 (13%)	4 (11%)	5 (12%)
Progression in CNS lesions only	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	7 (18%)	4 (11%)	6 (14%)
No progression during the trial*	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%)

Data are n (%). *Progression assessed according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

Table 3. **Progression by tumour site**

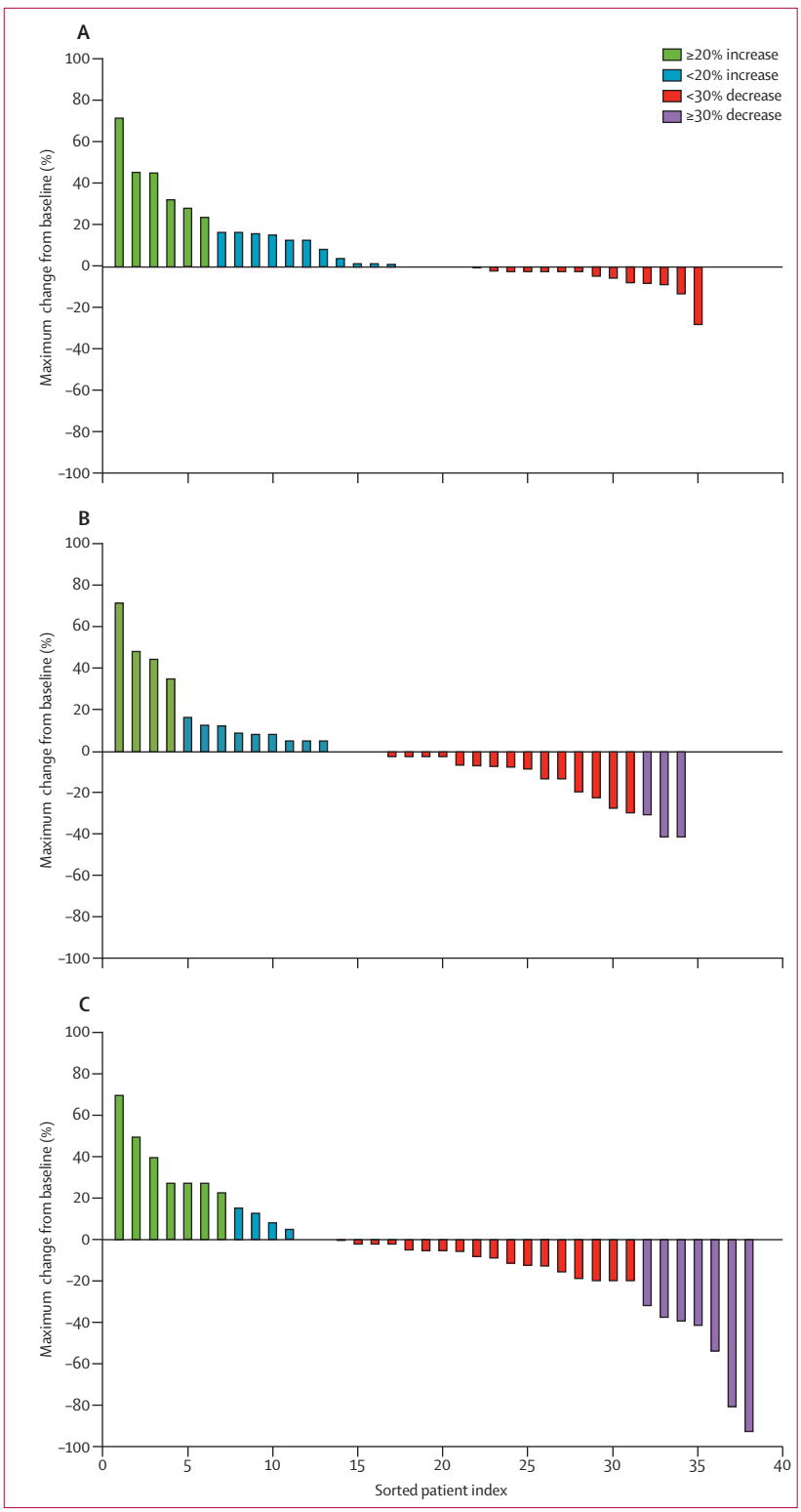

***Figure 3*: Change from baseline in size of CNS lesions**
Plots show the maximum change from baseline in the sum of the longest diameters of CNS target lesions with afatinib alone (A), afatinib plus vinorelbine (B), or investigator's choice of drug regimen (C).

Figure 3 shows the maximum change from baseline in the sum of the longest diameters of CNS target lesions in each treatment group. 35 patients were assessed in the afatinib alone group, 34 in the afatinib plus vinorelbine group, and 38 in the investigator's choice group. The proportion of patients who achieved an objective response in any lesion was less than 10% in each treatment group, except for patients with CNS lesions in the investigator's choice group (six [14%] of 43 patients; table 2). Of these six patients, we noted CNS responses in two (33%) patients receiving trastuzumab plus chemotherapy and four (67%) receiving lapatinib plus chemotherapy. Of patients in the investigator's choice group, extra-CNS responses were noted in two (5%) patients receiving lapatinib plus capecitabine (table 2). Disease control was similar for CNS lesions in all groups; for extra-CNS lesions, disease control ranged from 43% with afatinib alone to 61% with investigator's choice (table 2).

Treatment-related adverse events are shown in table 4. The most common grade 3 or 4 adverse events were diarrhoea (seven [18%] of 40 patients in the afatinib only group, nine [24%] of 37 patients in the afatinib plus vinorelbine group and two [5%] of 42 patients in the investigator's choice group) and neutropenia (none *vs* 14 [38%] *vs* four [10%]).

Treatment-related serious adverse events were reported in five (13%) of 40 patients given afatinib alone (decreased appetite, diarrhoea, vomiting, stomatitis, nausea, acute renal failure, and general physical health deterioration [n=1 for each except diarrhoea [n=3] and vomiting [n=2]); 11 (30%) of 37 patients given afatinib plus vinorelbine (lung infection, urosepsis, febrile neutropenia, anaemia, partial seizures, diarrhoea, vomiting, dysphagia, enteritis, stomatitis, rash, asthenia, mucosal inflammation, and pyrexia [n=1 for each except lung infection, febrile neutropenia, and asthenia [n=2], and diarrhoea [n=4]), and two (5%) of 42 patients given investigator's choice (one each of febrile neutropenia and diarrhoea). No treatment-related deaths occurred; however, three (8%) patients in the afatinib alone group, seven (19%) in the afatinib plus vinorelbine group, and five (12%) in the investigator's choice group had a non-treatment-related adverse event leading to death, mainly because of disease progression. The causes of these deaths were: deterioration of general physical health (n=5; one in the afatinib alone group, three in afatinib plus vinorelbine, and one in investigator's choice); malignant neoplasm progression (n=2; one in afatinib alone and one in investigator's choice); lung infection (one in afatinib alone); neurological symptoms (one in afatinib plus vinorelbine); metastatic neoplasm and neoplasm progression (one in afatinib plus vinorelbine); concomitant disease progression (n=2; one in afatinib plus vinorelbine and one in investigator's choice); and brain herniation (one in afatinib plus vinorelbine). Two deaths in the investigator's choice group occurred naturally (not as a result from an adverse event).

	Afatinib alone n=40			Afatinib plus vinorelbine n=37			Investigator's choice n=42		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any drug-related adverse event	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
Leucopenia	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 (%) of the safety population. Events are included in the table if reported for at least 10% of patients (grades 1–2) in any treatment group or for any grade 3 or 4 event that was reported in more than one patient. No treatment-related grade 5 events (ie, deaths) were reported. Additional grade 3–4 adverse events reported in the afatinib alone group were: conjuctivitis (one [3%]), skin lesion (one [3%]), generalised rash (one [3%]), acute renal failure (one [3%]), and general physical health deterioration (one [3%]). Additional grade 3–4 adverse events 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%]), raised serum alanine aminotransferase (one [3%]), low blood lymphocyte count (one [3%]) and low blood neutrophil count (one [3%]). Additional grade 3–4 adverse events reported in the investigator's choice group were: low white blood cell count (one [2%]) and abdominal pain (one [2%]).

Table 4: **Treatment-related adverse events**

Adverse events led to a dose reduction in 17 (43%) of 40 patients given afatinib alone, 16 (43%) of 37 patients given afatinib plus vinorelbine, and three (7%) of 42 patients given investigator' choice. Diarrhoea was the most common reason for dose reduction (nine [23%] patients in the afatinib alone group, 10 [27%] in the afatinib plus vinorelbine group, and one [2%] in the investigator's choice). Neutropenia resulted in a dose reduction in four (11%) patients in the afatinib plus vinorelbine group and in one (2%) patient in the investigator's choice group. Adverse events leading to discontinuation of study drugs were reported in four (10%) patients in the afatinib alone group, nine (24%) in the afatinib plus vinorelbine group, and nine (21%) in the investigator's choice group.

Discussion

In this study of patients with HER2-positive breast cancer with progressive brain metastases assigned to either afatinib, afatinib plus vinorelbine, or investigator's choice of treatment, roughly one-third of patients in each treatment group achieved clinical benefit, defined by absence of disease progression at any site for at least 12 weeks with no tumour-related worsening of neurological symptoms and no increase in corticosteroid dose. Although objective responses in the CNS were infrequent, the results suggest that the study treatments had slight activity for brain metastases in this heavily pre-treated population.

For context, in a phase 2 trial[9] in patients with HER2-positive metastatic breast cancer that had progressed after trastuzumab treatment, afatinib monotherapy resulted in objective responses in four (10%) of 41 treated patients and a median progression-free survival of 15·1 weeks. In the phase 3 LUX-Breast 1 trial[12] of patients with HER2-positive metastatic breast cancer who progressed on or after adjuvant or first-line trastuzumab, 154 (46%) of 334 patients given afatinib plus vinorelbine achieved an objective response and median progression-free survival was about 24 weeks. In both of these trials,[9,12] patients with active brain metastases were excluded. Therefore, the generally

lower number of responses and shorter progression-free survival in our trial might represent the difficulty in treating brain metastases. Moreover, the different patient populations enrolled in these studies should also be considered; eg, roughly 40% of patients in the LUX-Breast 1 trial were receiving afatinib plus vinorelbine as first-line treatment for advanced breast cancer whereas all patients in our trial had received previous treatment for advanced breast cancer.

Most patients in our study had disease progression in CNS lesions. This probably occurred because all patients in this study had to have a documented progression of their CNS lesions and at least one measurable CNS lesion before study entry, but the progression or presence of extra-CNS lesions was not required (only 41% of patients had extra-CNS target lesions). Therefore, some patients might have had stable (or well controlled) extra-CNS lesions at study entry. As such, most of the patients might have had aggressive or resistant disease in the brain with reduced drug penetration through their blood–brain barrier leading to frequent progression of the CNS lesions only, whereas the extra-CNS lesions, if present, often remained well controlled.

HER2-targeted agents are often given over several lines of treatment for HER2-positive metastatic breast cancer because results from two randomised trials[16–18] showed that continuation of trastuzumab is beneficial in patients whose cancer progresses during a trastuzumab-containing regimen, and giving a different anti-HER2 drug could still have substantial efficacy in patients whose cancer progresses on trastuzumab or other HER2-targeted drugs.[19,20] Although no formal proof exists that HER2-targeted drugs are effective in patients with brain metastases, retrospective analyses suggest that trastuzumab-containing regimens extend the survival of patients with CNS metastases.[21] To conclusively show proof of efficacy of HER2-targeted agents in this setting, afatinib and other HER2-targeted agents would need to be compared with a regimen without a HER2-targeted agent. However, similar to another randomised trial assessing lapatinib plus capecitabine versus lapatinib plus topotecan in patients with brain metastases,[22] our trial design did not prohibit use of HER2-targeted agents as this might have been deemed unethical and would probably have hindered accrual to the study. Instead we chose to use an investigator's choice of regimen as a comparator.

The study was not powered to compare the treatment groups, but the results suggest that afatinib monotherapy or afatinib plus vinorelbine did not provide better outcomes than the investigator's choice of treatment. No objective responses were documented in the afatinib alone group. As expected, the investigators' treatment choices were heterogeneous in the absence of any approved treatment for this setting, but mostly consisted of trastuzumab, lapatinib, or both, given with chemotherapy, despite previous cancer progression with trastuzumab, lapatinib, or both. Our results do not contradict a hypothesis that some patients might benefit from the continuation of a HER2-targeted drug, with the addition of chemotherapy, despite previous progression on this drug. Quality of life, which was not assessed in our trial, would be another important endpoint to consider in future assessments of treatments for patients with breast cancer and brain metastases.

Trastuzumab penetrates poorly through an intact blood–brain barrier. One study[23] showed that trastuzumab concentrations achieved in the cerebrospinal fluid (CSF) were 420 times lower than serum concentrations; however, a higher CSF-to-serum ratio (1:76) was noted in patients who had received whole-brain radiation therapy. Trastuzumab uptake might also be greater in cancerous brain lesions where the blood–brain barrier is impaired. In one study[24] uptake of ^{89}Zr-labelled trastuzumab measured by PET was 17·5 times higher in patients with brain metastases versus patients with macroscopically normal brain tissue. Lapatinib does not substantially 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 might 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 shown efficacy in patients with NSCLC and brain metastases. In a subgroup analysis of the phase 3 LUX-Lung 3 trial,[29] median progression-free survival with afatinib was similar in patients with or without asymptomatic brain metastases (11·1 versus 13·7 months, respectively). In a compassionate-use programme with afatinib, the median time to treatment failure for patients with pretreated NSCLC and CNS metastasis (3·6 months) did not differ from a matched group of 100 patients without CNS metastases.[30] 11 of the 31 assessable patients with NSCLC had a CNS response to afatinib, and most had controlled cerebral disease. One patient with an impressive response had an afatinib concentration in the CSF of nearly 1 nM.[30] Although this concentration is probably sufficient to inhibit EGFR and HER4, this concentration is less than the half maximum inhibitory concentration for HER2 (14 nM). Thus, the concentration achieved in the CSF in our 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 or 4 adverse events in our study was high. Discontinuation of afatinib in the afatinib alone treatment group because of adverse events was infrequent (four [10%] patients), but 17 (43%)

had a dose reduction, compared with only three (7%) of the 42 patients who received investigator's choice. This difference is not unexpected because afatinib had a well described dose reduction protocol, whereas dose reductions for drugs used in the investigator's choice, such as trastuzumab, were not foreseen on the basis of their prescribing information. Most patients assigned to afatinib alone had diarrhoea and seven (18%) of 40 patients had grade 3 diarrhoea, suggesting that early treatment with loperamide or other drugs for the management of diarrhoea is important for patients receiving afatinib. Overall, no unexpected adverse events were noted and the adverse events that did occur were generally manageable; however, the investigator's choice regimens seemed to be better tolerated, especially when compared with afatinib plus vinorelbine.

In conclusion, about one-third of patients benefited from the HER2-targeted regimens. No objective responses were achieved in patients treated with afatinib alone, but around one-third of patients, including those treated with afatinib alone, did not have disease progression during the first 12 weeks. Overall, afatinib-containing treatments did not have better activity than investigator's choice treatments and also seemed to be less well tolerated. No further development of afatinib for HER2-positive breast cancer is currently planned.

Contributors

AS, MO-K, and HJ conceived and designed the study. MO-K and HJ did the literature search. VD, JR, TB, ELR, ME, S-BK, AS, JHS, P-LK-L, JT, FP, PB, and HJ obtained the data. JC, VD, JR, JB, TB, SH, ME, AS, J-MN, P-LK-L, JT, FP, EC, and PB recruited the patients. JC, VD, JR, JB, SH, S-BK, AS, J-MN, PB, MO-K, FR, and HJ analysed and interpreted the data. All authors were involved in drafting and reviewing 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 from Roche and Celgene as compensation for advice. P-LK-L has received a grant from Boehringer Ingelheim, as stated in the manuscript. FP has participated in clinical research funded by 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 and FR are employees of Boehringer Ingelheim. HJ has received money to his institution and honoraria for consultancy roles from BluePrint Medicines, Ariad Pharmaceuticals, and Orion Pharma. All other authors declare no competing interest.

Acknowledgments

This study was funded by Boehringer Ingelheim Pharmaceuticals, Inc. Editorial assistance and medical writing services, supported financially by Boehringer Ingelheim Pharmaceuticals, Inc, were provided by Christine Arris and Caroline Allinson of GeoMed (Macclesfield, UK), an Ashfield company, part of UDG Healthcare plc, during the preparation of this manuscript.

References

1 Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2014; **32:** 2100–08.

2 Gori S, Rimondini S, De Angelis V, et al. Central nervous system metastases in HER-2 positive metastatic breast cancer patients treated with trastuzumab: incidence, survival, and risk factors. *Oncologist* 2007; **12:** 766–73.

3 Melisko ME, Moore DH, Sneed PK, De Franco J, Rugo HS. Brain metastases in breast cancer: clinical and pathologic characteristics associated with improvements in survival. *J Neurooncol* 2008; **88:** 359–65.

4 Eichler AF, Kuter I, Ryan P, Schapira L, Younger J, Henson JW. Survival in patients with brain metastases from breast cancer: the importance of HER-2 status. *Cancer* 2008; **112:** 2359–67.

5 Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol* 2013; **14:** 64–71.

6 Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol* 2008; **26:** 1993–99.

7 Lin NU, Dieras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res* 2009; **15:** 1452–59.

8 Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene* 2008; **27:** 4702–11.

9 Lin NU, Winer EP, Wheatley D, et al. A phase II study of afatinib (BIBW 2992), an irreversible ErbB family blocker, in patients with HER2-positive metastatic breast cancer progressing after trastuzumab. *Breast Cancer Res Treat* 2012; **133:** 1057–65.

10 Bahleda R, Soria J, Berge Y, et al. Phase I trial assessing safety and pharmacokinetics of afatinib (BIBW 2992) with intravenous weekly vinorelbine in advanced solid tumors. *J Clin Oncol* 2011; **29** (suppl)**:** 2585 (abstr).

11 Mukai H, Masuda N, Ishiguro H, et al. Phase I trial of afatinib plus vinorelbine in Japanese patients with advanced solid tumors including breast cancer. *Cancer Chemother Pharmacol* 2015; **76:** 739–50.

12 Harbeck N, Huang C-S, Hurvitz SA, et al. Randomized phase III trial of afatinib plus vinorelbine versus trastuzumab plus vinorelbine in patients with HER2-overexpressing metastatic breast cancer who had progressed on one prior trastuzumab treatment: LUX-Breast 1. *Cancer Res* 2015; **75:** P5-19-01 (abstr).

13 Yang JC, Shih JY, Su WC, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. *Lancet Oncol* 2012; **13:** 539–48.

14 Solca F, Dahl G, Zoephel A, et al. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. *J Pharmacol Exp Ther* 2012; **343:** 342–50.

15 Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. *Cancer Treat Rep* 1985; **69:** 1375–81.

16 von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a German breast group 26/breast international group 03–05 study. *J Clin Oncol* 2009; **27:** 1999–2006.

17 von Minckwitz G, Schwedler K, Schmidt M, et al. Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. *Eur J Cancer* 2011; **47**: 2273–81.

18 Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. *J Clin Oncol* 2012; **30:** 2585–92.

19 Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006; **355:** 2733–43.

20 Krop IE, Kim SB, Gonzalez-Martin A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; **15:** 689–99.

21 Mehta AI, Brufsky AM, Sampson JH. Therapeutic approaches for HER2-positive brain metastases: circumventing the blood-brain barrier. *Cancer Treat Rev* 2013; **39:** 261–69.

22 Lin NU, Eierman W, Greil R, et al. Randomized phase II study of lapatinib plus capecitabine or lapatinib plus topotecan for patients with HER2-positive breast cancer brain metastases. *J Neurooncol* 2011; **105:** 613–20.

23 Stemmler HJ, Schmitt M, Willems A, Bernhard H, Harbeck N, Heinemann V. Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood-brain barrier. *Anticancer Drugs* 2007; **18:** 23–28.

24 Dijkers EC, Oude Munnink TH, Kosterink JG, et al. Biodistribution of 89Zr-trastuzumab and PET imaging of HER2-positive lesions in patients with metastatic breast cancer. *Clin Pharmacol Ther* 2010; **87:** 586–92.

25 Polli JW, Humphreys JE, Harmon KA, et al. The role of efflux and uptake transporters in [N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino }methyl)-2-furyl]-4-quinazolinamine (GW572016, lapatinib) disposition and drug interactions. *Drug Metab Dispos* 2008; **36:** 695–701.

26 Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. *J Clin Oncol* 2004; **22:** 3608–17.

27 Tomasello G, Bedard PL, de Azambuja E, Lossignol D, Devriendt D, Piccart-Gebhart MJ. Brain metastases in HER2-positive breast cancer: the evolving role of lapatinib. *Crit Rev Oncol Hematol* 2010; **75:** 110–21.

28 Leyland-Jones B. Human epidermal growth factor receptor 2-positive breast cancer and central nervous system metastases. *J Clin Oncol* 2009; **27:** 5278–86.

29 Schuler M, Yang JC, Sequist LV, et al. Efficacy of afatinib vs chemotherapy in treatment-naive patients with non-small cell lung cancer (NSCLC) harbouring activating EGFR mutations with or without metastatic brain disease. *J Thorac Oncol* 2013; **8** (suppl 2): S299 (abstr MO07.13).

30 Hoffknecht P, Tufman A, Wehler T, et al. Efficacy of the irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease. *J Thorac Oncol* 2015; **10:** 156–63.