available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Erlotinib in combination with capecitabine and docetaxel in patients with metastatic breast cancer: A dose-escalation study ☆

Chris Twelves[a,c,*], *José M. Trigo*[b], *Rob Jones*[c], *Flavio De Rosa*[d], *Ashok Rakhit*[e], *Scott Fettner*[e], *Tonya Wright*[c], *José Baselga*[b]

[a]*University of Leeds and St. James Hospital, Leeds, United Kingdom*
[b]*Medical Oncology Service, Vall D'Hebron University Hospital, Barcelona, Spain*
[c]*Beatson Oncology Centre, Glasgow, United Kingdom*
[d]*F. Hoffmann-La Roche, Basel, Switzerland*
[e]*F. Hoffmann-La-Roche, Nutley, New Jersey, United States*

ARTICLE INFO

Article history:
Received 17 July 2007
Received in revised form 15 November 2007
Accepted 20 December 2007

Keywords:
Erlotinib
Capecitabine
Docetaxel
Metastatic breast cancer (MBC)
Dose-escalation
Pharmacokinetics
Triple-drug combination
Maximum-tolerated dose (MTD)

ABSTRACT

Capecitabine added to docetaxel extends survival in metastatic breast cancer (MBC) and shows additive efficacy with erlotinib in pre-clinical studies. This study aimed to determine the maximum-tolerated dose (MTD) of capecitabine/docetaxel with erlotinib and assess tolerability, anti-tumour activity and potential pharmacokinetic interactions.

Three treatment cohorts were assessed, using different dosing regimens. A total of 24 women with MBC were enrolled sequentially. The regimen comprising erlotinib 100 mg/day continuously, capecitabine 825 mg/m^2 bid on days 1 to 14 and docetaxel 75 mg/m^2 intravenously every 3 weeks on day 1 was well tolerated and was established as the MTD. Overall response rate was 67%, comprising two complete and 12 partial responders in 21 assessable patients. The most common treatment-related adverse events were gastrointestinal disorders and skin toxicities. Pharmacokinetic studies showed that exposure to the three drugs was not reduced when given in combination. These encouraging preliminary results warrant further trials of the combination in MBC.

1. Introduction

Approximately 30–40% of breast cancer patients will develop metastatic disease that is incurable with current therapies.[1] New treatments that improve survival and quality of life are urgently needed[2] and the epidermal growth factor receptor (EGFR) superfamily is an attractive therapy target.[3]

HER1/EGFR dysregulation has a pivotal role in the growth and progression of many different cancers, including breast cancer,[4–6] and has been linked to metastasis, advanced dis-

☆ This work has been previously presented in part at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Boston, USA.

* *Corresponding author:* Present address: Professor of Clinical Pharmacology and Oncology and Deputy Director, Cancer Research UK Clinical Centre in Leeds, Cancer Research Building, St. James Hospital, Beckett Street, Leeds, UK. Tel.: +0113 2067195.
E-mail address: c.j.twelves@leeds.ac.uk (C. Twelves).

0959-8049/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.ejca.2007.12.011

ease and a poor prognosis.[5,7,8] Erlotinib (Tarceva®) is a highly potent, orally active, reversible inhibitor of HER1/EGFR tyrosine kinase, with activity against a wide range of solid tumour types, including locally advanced and metastatic breast cancer (MBC).[9–14] Recently, a phase III trial demonstrated that erlotinib, in combination with gemcitabine, produced a modest, although statistically significant improvement in survival in patients with advanced pancreatic cancer.[15]

Both docetaxel (Taxotere®) and capecitabine (Xeloda®) have proven activity in MBC.[16–21] In combination, they increase response rate, progression-free survival and overall survival compared with docetaxel alone, and represent an established treatment option for anthracycline-resistant MBC.[22] A capecitabine/docetaxel/erlotinib triple-drug combination combines different mechanisms of action, with limited overlap in toxicity, and may offer enhanced efficacy, especially in women with HER2-negative breast cancer.

This study investigated the tolerability of erlotinib in combination with docetaxel and capecitabine in patients with MBC, and provided a preliminary evaluation of its anti-tumour efficacy.

2. Patients and methods

The primary objective was to determine the maximum-tolerated dose (MTD) of capecitabine and docetaxel with erlotinib in women with locally advanced breast cancer or MBC. Secondary objectives included the evaluation of tolerability and anti-tumour efficacy of the triple-drug combination, and any potential pharmacokinetic interactions.

2.1. Patient population

Eligible patients were female, $\geqslant$18 years, with histologically confirmed, incurable, locally advanced breast cancer or MBC. Key inclusion criteria included measurable disease, $\leqslant$1 previous chemotherapy regimen for advanced/metastatic disease (patients may also have had adjuvant chemotherapy), Eastern Cooperative Oncology Group (ECOG) performance status 0–1, and adequate haematologic, hepatic and renal function. Patients were ineligible if they had received prior docetaxel or HER-targeted therapy; radio-, immuno- or chemotherapy within the previous 28 days, or if they had any unresolved treatment-related toxicities. Other exclusion criteria included pregnancy; life expectancy <12 weeks; central nervous system disorders; unstable systemic disease; cardiac disease or other primary malignancies.

All patients provided signed informed consent. The study was conducted according to the latest version of the Declaration of Helsinki and in compliance with the UK and Spanish local laws and regulations; it adhered to the International Conference on Harmonisation guidelines for Good Clinical Practice. The protocol and amendments were reviewed by local ethics committees.

2.2. Treatment plan

This was a phase Ib, open-label, dose-escalation study conducted in two study centres. Patients were to be enrolled sequentially in up to six treatment cohorts (Fig. 1, A–F). Due to potentially overlapping toxicities of erlotinib and capecitabine, a lower dose of both drugs was initially administered (100 mg/day and 825 mg/m^2 twice daily [bid], respectively). The first patient was to be treated in cohort A for one cycle (21 days) with 100 mg/day erlotinib continuously, capecitabine 825 mg/m^2 bid days 1 to 14 and docetaxel 60 mg/m^2 on day 1, repeated every 3 weeks. If no DLTs had occurred by day 14, two further patients were to be treated. Subsequent cohorts comprised six patients, with the first patient in each cohort treated for 2 weeks before the remaining patients were enrolled. Dose-escalation to the next cohort was based on the toxicities observed during the first cycle of treatment.

Patients received up to six cycles of therapy; treatment was discontinued in the event of progressive disease, serious toxicity or at the patient's request. Patients with objective responses or stable disease after six cycles could receive further treatment until disease progression or unacceptable toxicity in an extension phase of the study.

2.3. Study treatment

Erlotinib hydrochloride (25 mg, 100 mg, 125 mg tablets) and capecitabine (150 mg, 500 mg tablets) were supplied by F. Hoffmann-La Roche Ltd. Commercial docetaxel was supplied as 20 mg and 80 mg intravenous vials. Capecitabine was taken orally, bid (12-h interval), for 14 days. Docetaxel was administered as a 1-h infusion on the first day of each 3-week cycle. Erlotinib was taken daily before chemotherapy, except during cycle 1 in which erlotinib therapy commenced 24 h after the first treatment with capecitabine and docetaxel.

Patients were pre-medicated with oral corticosteroids for 3 days, starting 1 day before docetaxel administration. Concomitant administration of CYP3A4 inducers or inhibitors was permitted with caution.

2.4. Dose-limiting toxicities, determination of maximum-tolerated dose and dose modifications

A DLT was defined as one or more of the following: $\geqslant$grade 3 non-haematologic toxicity; thrombocytopaenia (platelets $\leqslant 25.0 \times 10^9$/l); grade 4 neutropaenia for $\geqslant$5 days duration or febrile neutropaenia; any toxicity necessitating the interruption of erlotinib administration during cycle 1; any other laboratory abnormality occurring during cycle 1 requiring a dose reduction.

If three or more of the patients in a cohort had a DLT (the DLT cohort), then the preceding cohort (the MTD cohort) was to be expanded step-wise to 12 patients to confirm tolerability of the MTD.

Dose modifications and interruptions were specified for the study drugs depending upon the type and severity of toxicities. Skin toxicities were managed by dose delay/reduction. Diarrhoea was managed with loperamide and, if necessary, the interruption of capecitabine treatment.

2.5. Study assessments

At screening (within 28 days of day 1), patients underwent a full clinical assessment. A tumour assessment of all disease

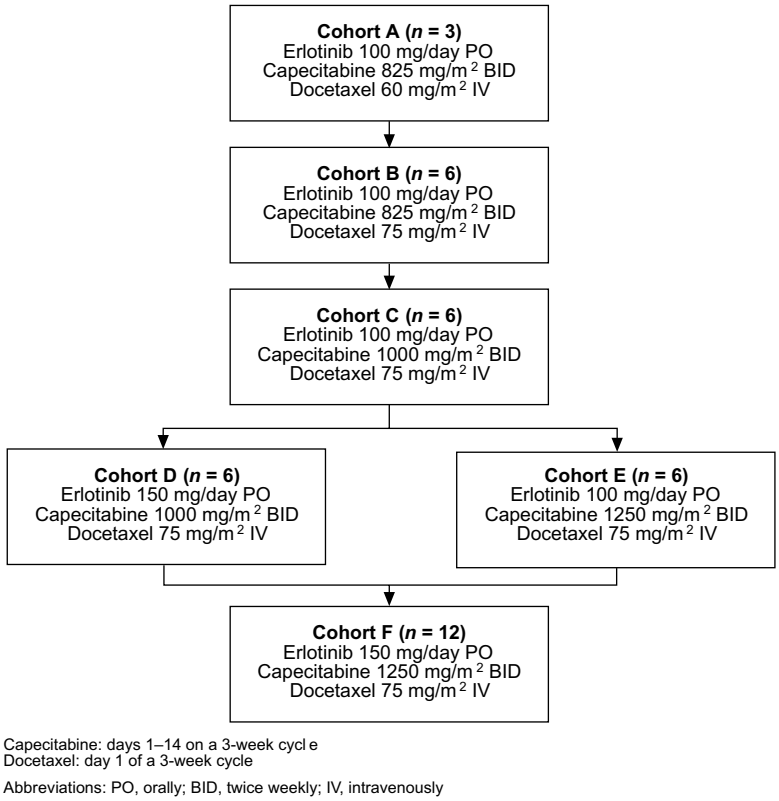

Fig. 1 – Overall study design and planned patient accrual.

sites was also made. Other screening assessments included standard laboratory tests; plasma concentration of α-1-acid glycoprotein (AAG) and plasma concentration of EGF.

Patients were assessed during the week prior to therapy and before each cycle (including physical examination, body weight measurement, laboratory assessments and ECOG performance status). Tumour assessments were made after every two cycles. Adverse events (AEs) were recorded throughout the study, using the National Cancer Institute – Common Toxicity Criteria (NCI-CTC), version 2.0.

2.6. *Pharmacokinetics*

Pharmacokinetic parameters were evaluated for capecitabine and docetaxel after administration together (cycle 1, day 1), after erlotinib alone (cycle 1, day 21) and after all three study drugs were administered in combination (cycle 2, day 1). Blood samples were, therefore, taken on days 1, 2, 21, 22, 23 and 36 from patients in cohorts A and B. An additional sample was collected from any patient with a serious AE.

On sampling days, 2 ml (capecitabine, docetaxel) or 3 ml (erlotinib) blood samples (from the non-infusion arm) were collected into a tube containing either EDTA (capecitabine, docetaxel) or lithium heparin (erlotinib), and were placed immediately on ice. Within an hour, the samples were centrifuged at 1500 rpm (capecitabine, docetaxel) or 2000 rpm (erlotinib) for 10 min at 4 °C, and plasma was immediately transferred to storage tubes, which were then stored at −70 °C before analysis.

Measurements of docetaxel and erlotinib concentrations in plasma samples were performed by MDS Pharma (St. Laurent, Montreal, Quebec, Canada). Docetaxel was isolated from plasma by protein precipitation extraction and was determined by HPLC with mass spectrometric detection. Erlotinib was isolated from plasma by liquid/liquid extraction and determined by HPLC with mass spectrometric detection. Measurements of capecitabine concentrations in plasma samples were performed by Advion BioSciences, Inc. (Ithaca, NY, USA). Capecitabine was isolated from plasma by a protein precipitation method followed by solid-phase extraction. The supernatant from the solid-phase extraction was analysed by turbo ion spray liquid chromatography/tandem mass spectrometry.

The quality of the determinations for capecitabine, docetaxel and erlotinib was satisfactory throughout. The lower limit of quantification was 5.02 ng/ml for docetaxel and 1 ng/ml for capecitabine and erlotinib. Assay precision (coefficient of variation) determined from quality control samples was below 16.4% for capecitabine, below 15.2% for docetaxel and below 6.9% for erlotinib. Accuracy was between 92.3% and 106.2% for capecitabine, whereas for docetaxel and erlotinib, accuracy was better than 117.5% and 107.6%, respectively.

The following pharmacokinetic parameters were evaluated for the three study drugs and certain metabolites (OSI-420 + OSI-413 for erlotinib; 5′DFUR and 5-FU for capecitabine): maximum observed plasma concentration (C_{max}), time to C_{max}, and area under the plasma concentration–time curve. Each pharmacokinetic parameter was compared between erlotinib/chemotherapy administration alone anf in combination.

2.7. Tumour response

Response was assessed every 6 weeks, using the Response Evaluation Criteria in Solid Tumours (RECIST).[23] The best response achieved between treatment start and disease progression was recorded. A confirmed responder was defined as a patient having a complete response (CR) or partial response (PR) for at least four consecutive weeks at any time during treatment.

3. Results

3.1. Patient characteristics and treatment

Twenty-four women were enrolled and assigned sequentially to the three cohorts (A, B, C). Patient and disease characteristics are shown in Table 1.

Table 1 – Patient characteristics at baseline

	Cohort A	Cohort B	Cohort C[a]
No. of patients	6	12	6
Age (years)	49.5	51.5	54
Median (range)	(38–61)	(40–63)	(50–58)
Eastern Cooperative Oncology Group performance status			
0	4	7	3
1	2	5	3
Disease stage			
Locally advanced	0	2	0
Metastatic	6	10	6
Prior treatment (no. of patients)			
Chemotherapy[b]	5	12	6
Radiotherapy	3	11	5
Hormonal therapy	4	6	3
Histologic grade of primary tumour			
Well differentiated	0	0	2
Moderately differentiated	1	5	1
Poorly differentiated	3	7	3
Anaplastic	0	0	0
Unknown	2	0	0
Oestrogen receptor status of primary tumour (status of metastatic tumour)			
Positive	2 (2)	6 (0)	3 (2)
Negative	3 (1)	5 (0)	2 (1)
Unknown	1 (3)	1 (12)	1 (3)
Progesterone receptor status of primary tumour (status of metastatic tumour)			
Positive	2 (1)	4 (0)	2 (3)
Negative	2 (1)	4 (0)	2 (0)
Unknown	2 (4)	4 (12)	2 (3)
HER2 status[c]			
0	2	4	2
1+	3	5	0
2+	0	2	1
3+	1	0	2

a Six patients entered this cohort; however, one patient was assigned the wrong dose and is not included for the purpose of determining dose-limiting toxicity of the cohort.

b In the majority of patients, chemotherapy was given in the adjuvant or neoadjuvant setting.

c Cohort B, $n = 11$; Cohort C, $n = 5$.

All patients received at least one dose of erlotinib in combination with capecitabine and docetaxel; 18 completed the full planned six cycles of treatment, and five received more than six cycles. Overall exposure to trial medication was similar across cohorts. In cohorts A, B and C, exposure to daily erlotinib ranged from 61 to 186, 40 to 249 and 1 to 165 days, respectively. For capecitabine, patients were treated for a range of four to >six cycles, three to >six cycles and one to >six cycles, respectively. Exposure to docetaxel ranged from four to >six cycles, three to >six cycles and six to >six cycles, respectively.

3.2. Determination of MTD

There were no DLTs in cohorts A and B; six patients were subsequently enrolled into cohort C (erlotinib 100 mg/day; capecitabine 1000 mg/m^2 bid; docetaxel 75 mg/m^2 intravenously). During the first cycle, DLTs were reported in three of these six patients: one had grade 3 febrile neutropaenia, the second had grade 3 diarrhoea and grade 3 lethargy and the third had grade 3 diarrhoea. The patient with febrile neutropaenia subsequently received a reduced dose of capecitabine (825 mg/m^2 bid) and docetaxel (60 mg/m^2) without further DLTs. One patient with grade 3 diarrhoea withdrew consent on day 11. Erlotinib and capecitabine were stopped for 13 and 7 days, respectively, in cycle 1 for the third patient with DLTs. The doses of all three study drugs were then reduced in cycle 2 (erlotinib: 50 mg/day; capecitabine: 825 mg/m^2 bid; docetaxel: 55 mg/m^2); doses were not escalated further and no further DLT was seen. As more than one-third of the patients had DLTs, cohort C was designated the DLT cohort. One patient in cohort C had grade 2 cutaneous rash from day 12, and the dose of erlotinib was reduced to 75 mg/day from day 42 onwards.

Cohort B was, therefore, expanded to 12 patients to confirm tolerability, and erlotinib 100 mg/day, capecitabine 825 mg/m^2 bid with docetaxel 75 mg/m^2 intravenously was confirmed as the MTD. The only significant toxicities observed within the expanded cohort B were four patients who experienced grade 3 neutropaenia, grade 3 asthenia, hyperbilirubinaemia or grade 2 diarrhoea (all during cycle 3). Two dose reductions of capecitabine were required for the patient with grade 2 diarrhoea (to 650 mg/m^2 bid and to 485 mg/m^2 bid). For the patient with asthenia, doses of both docetaxel and capecitabine were reduced by 27% and 23%, respectively. These modified doses were then tolerated for cycles 3–6.

3.3. Tolerability

All patients experienced at least one treatment-related AE, mainly grade 1 or grade 2; the most common were diarrhoea and rash. Diarrhoea was reported in 83% of patients in cohort A and in all patients in cohorts B and C. Treatment-related rash was reported in 83% of patients across all cohorts. There was no correlation between erlotinib exposure (C_{max} on day 1, cycle 2) and the maximum intensity of diarrhoea and rash (data not shown).

The overall rate of severe (grade 3 or grade 4) AEs was relatively low, but the rate of grade 3 events did increase across cohorts (17%, 42% and 66% in cohorts A, B and C, respectively;

Table 2). Grade 3 toxicities included: diarrhoea, rash, lethargy, asthenia and febrile neutropaenia. Three patients (one in each cohort) experienced grade 4 toxicity: neutropaenia, hepatic vein thrombosis and acute renal failure. The latter two events were not considered treatment-related. Eleven serious AEs were reported in five patients; most were considered unrelated to treatment, except for pharyngeal candidiasis and neutropaenic sepsis in a patient in cohort B (probably related), and febrile neutropaenia in one patient in cohort C.

The most frequently occurring grade 3/4 laboratory abnormalities were leucopaenia/neutropaenia. Grade 4 neutropaenia occurred in four patients in cohort A (66%), eight in cohort B (66%) and five in cohort C (83%). Grade 3/4 neutropaenic sepsis and febrile neutropaenia were observed in one patient in cohorts B and C, respectively. Both were considered treatment-related and resolved with antibiotic treatment.

Grade 1/2 conjunctivitis in 33% (cohorts A and B) and 50% (cohort C) of patients was the most common ophthalmologic AE, but was not clinically disturbing, so specific measures were not required. In most cases, these AEs were considered probably treatment-related. No clinically significant changes were observed in vital signs, body weight or electrocardiogram readings. For the majority of patients ECOG performance status remained unchanged from baseline whilst on therapy.

There were no drug-related deaths. Two patients in cohort A were withdrawn due to AEs. One 38-year-old patient withdrew after 98 days due to grade 2 hepatotoxicity (onset on day 7), considered probably treatment-related. She received full-dose erlotinib for 98 days and docetaxel (full dose) only for cycles 1–3. Capecitabine was given at full dose (825 mg/m^2 bid) in cycles 1, 2 and 3 for 14, 5 and 7 days, then reduced to 650 mg/m^2 bid in cycle 4 (7 days). The second patient (58 years old) developed a grade 2 pustular rash on day 23, considered possibly treatment-related. This patient remained on the study drugs without dose modification or interruption. The rash was not treated and it persisted when the patient was discontinued from the study on day 64.

3.4. *Pharmacokinetics*

The pharmacokinetic analyses for erlotinib were based on the patients in cohorts A and B following treatment with erlotinib alone (cycle 1, day 21) and in combination with docetaxel and capecitabine (cycle 2, day 1; Table 3). There were no clear differences between the parameters during erlotinib monotherapy or concomitant dosing with docetaxel and capecitabine, or between different docetaxel dose levels. At the MTD (cohort B), co-administration of capecitabine and docetaxel had no significant effect on the pharmacokinetics of erlotinib (Fig. 2) or its metabolites (data not shown). Furthermore, the mean plasma concentrations of docetaxel and capecitabine (and its metabolites; data not shown) did not change when administered in the triple-drug combination (Table 3). However, a decrease in the C_{max} of docetaxel was observed following concomitant administration with erlotinib. Baseline AAG concentration was weakly correlated with erlotinib exposure, but no notable relationship was observed between erlotinib exposure and baseline EGF concentrations.

Table 2 – Summary of treatment-related adverse events with at least one grade 3 or 4 toxicity in any cohort

	No. of patients					
	Cohort A, $n = 6$		Cohort B, $n = 12$		Cohort C, $n = 6$	
	All grades (%)	Grades 3/4 (%)	All grades (%)	Grades 3/4 (%)	All grades (%)	Grades 3/4 (%)
Gastrointestinal disorders						
Diarrhoea	5 (83)	0	12 (100)	0	6 (100)	2 (33)
Constipation	1 (17)	1 (17)	0	0	1 (17)	0
Abdominal pain NOS	0	0	4 (33)	1 (8)	0	0
Mouth ulceration	1 (17)	0	1 (8)	0	2 (33)	1 (17)
Skin and subcutaneous tissue disorders						
Rash	5 (83)	1 (17)	10 (83)	0	5 (83)	1 (17)
General disorders and administration site conditions						
Asthenia	3 (50)	0	6 (50)	1 (8)	3 (50)	0
Mucosal inflammation NOS	2 (33)	0	8 (75)	0	2 (33)	1 (17)
Lethargy	0	0	5 (42)	1 (8)	2 (33)	1 (17)
Infections and infestations						
Neutropaenic sepsis	0	0	1 (8)	1 (8)	0	0
Metabolism and metabolic disorders						
Hypokalaemia	0	0	1 (8)	1 (8)	0	0
Hepatobiliary disorders						
Hyperbilirubinaemia	1 (17)	0	0	0	2 (33)	2 (33)
Blood and lymphatic system disorders						
Febrile neutropaenia	0	0	0	0	1 (17)	1 (17)
Neutropaenia	1 (17)	1 (17)	0	0	0	0

Abbreviation: NOS, not otherwise specified.

Table 3 – Mean (±SEM) pharmacokinetic parameters for erlotinib, docetaxel and capecitabine

Parameter (U)	Oral erlotinib (100 mg/day)				Intravenous docetaxel				Oral capecitabine (825 mg/m^2 bid)			
	Cohort A		Cohort B		Cohort A (60 mg/m^2)		Cohort B (75 mg/m^2)		Cohort A		Cohort B	
	Monotherapy	Combination[a,b]	Monotherapy	Combination[a,b]	With capecitabine[b]	With capecitabine and erlotinib[c]	With capecitabine[b]	With capecitabine and erlotinib[c]	With docetaxel[a]	With docetaxel and erlotinib[c]	With docetaxel[a]	With docetaxel and erlotinib[c]
Visit	Cycle 1, day 21 $n = 6$	Cycle 2, day 1 $n = 6$	Cycle 1, day 21 $n = 10$[d]	Cycle 2, day 1 $n = 10$[d]	Cycle 1, day 1 $n = 3$[e]	Cycle 2, day 1 $n = 3$[e]	Cycle 1, day 1 $n = 9$[f]	Cycle 2, day 1 $n = 9$[f]	Cycle 1, day 1 $n = 5$	Cycle 2, day 1 $n = 5$	Cycle 1, day 1 $n = 9$[g]	Cycle 2, day 1 $n = 9$[g]
C_{max} (ng/ml)	1632 ± 225	1497 ± 184	1593 ± 152	1510 ± 152	1807 ± 248	1513 ± 217	2722 ± 244	2247 ± 144	3790 ± 649	2414 ± 429	6274 ± 2045	3934 ± 823
T_{max} (h)	4.35 ± 1.11	3.89 ± 0.47	3.49 ± 0.86	4.07 ± 1.09	0.94 ± 0.10	1.00 ± 0.00	0.8421 ± 0.08	0.77 ± 0.06	0.80 ± 0.20	1.11 ± 0.29	1.07 ± 0.17	1.31 ± 0.29
$AUC_{(last)}$ (ng h/ml)	27,137 ± 4649	25,691 ± 3421	26,201 ± 3576	25,623 ± 3408	2080 ± 339	1767 ± 264	3083 ± 222	2720 ± 308	3310 ± 412	3885 ± 169	5159 ± 1037	5264 ± 774
$AUC_{(0-24\ h)}$(ng h/ml)	27,137 ± 4984	25,141 ± 3310	26,118 ± 3527	25,400 ± 3337	2104 ± 317	1767 ± 264	3097 ± 221	2723 ± 307	3315 ± 412	3886 ± 169	5162 ± 1036	5268 ± 774

Abbreviations: AUC, area under the plasma concentration–time curve; C_{max}, maximum observed plasma concentration; SEM, standard error of the mean; T_{max}, time to C_{max}.

a In combination with intravenous docetaxel (60 mg/m^2 in cycle 2, cohort A; 75 mg/m^2 in cycle 2, cohort B).

b In combination with oral capecitabine (825 mg/m^2 bid, both cohorts).

c Erlotinib administered at 100 mg/day.

d Pharmacokinetic results from two patients excluded due to the lack of available data in both periods.

e Pharmacokinetic results from two patients excluded due to implausibly high concentrations in a single period, possibly as a result of non-separable peaks from impurities present in the plasma samples. Results from a further patient were also excluded due to a longer infusion time (3 h) and therefore the sampling scheme was modified.

f Pharmacokinetic results from two patients excluded due to implausibly high concentrations in a single period, and from one patient due to the lack of available data in both periods.

g Pharmacokinetic results from three patients are not included due to the lack of available data in both periods.

Fig. 2 – Plasma concentration–time curves for erlotinib, during monotherapy (sampled on day 21 of cycle 1) and in combination with docetaxel and capecitabine (day 1, cycle 2) at the maximum-tolerated dose. Patients received erlotinib (100 mg/day), capecitabine 825 mg/m^2 twice daily + docetaxel 75 mg/m^2 intravenously (every 3 weeks). Values are means and standard errors.

Table 4 – Best tumour response to treatment with erlotinib in combination with docetaxel and capecitabine

	No. of patients			
	Cohort A, $n = 6$[a]	Cohort B, $n = 12$[a]	Cohort C, $n = 6$[a]	Total, $n = 24$
Evaluable patients	5	11	5	21
Complete response	0	2	0	2
Partial response	3	5	4	12
Stable disease	2	2	1	5
Progressive disease	0	2	0	2

a Overall response data were not available for one patient in each cohort.

3.5. *Anti-tumour efficacy*

Overall tumour response was assessed in 21 patients and best response to treatment is summarised in Table 4. The overall response rate was 67%, comprising 12 PRs, (in 60%, 45% and 80% of patients in cohorts A, B and C, respectively) and two CRs (patients with soft-tissue metastases in cohort B). Time to disease progression varied across the cohorts, ranging from 148 to 169 days in cohort A, 78 to 253 days in cohort B and 122 to 129 days in cohort C.

4. Discussion

This study has established that erlotinib (100 mg/day) can be combined with capecitabine at 825 mg/m^2 bid and docetaxel 75 mg/m^2 (every 3 weeks) in patients with locally advanced

breast cancer or MBC. The combination was generally well tolerated and the response rate of 67% is encouraging. Moreover, although the two-drug combination of capecitabine and docetaxel is highly active, frequent dose modifications are often required,[22,24] so combining a potentially active third agent at the expense of a modest reduction in capecitabine dose may be attractive. The dose of erlotinib defined for this combination is lower than that used as a single agent (100 mg/day and 150 mg/day, respectively). This is, however, the same dose of erlotinib that, in combination with gemcitabine, demonstrated greater activity in pancreatic cancer than gemcitabine alone.

In previous phase I/Ib trials, erlotinib was well tolerated when given in combination with chemotherapy agents, including taxanes and platinum compounds.[9,25–30] In this study, the toxicity profile of the triple-drug combination was acceptable, and only two patients were withdrawn due to toxicity (one probably and one possibly treatment-related). As expected, toxicity increased as drug doses were escalated, but there was no evidence of cumulative toxicity, with 18 out of 24 (75%) patients completing the full six cycles of planned treatment. Importantly, there were no drug-related deaths.

Toxicity was manageable and corresponded to the expected toxicities of the three drugs, namely diarrhoea, nausea, vomiting and rash.[11–13,16–21,31] Consistent with previous reports, the severity of most episodes of rash and diarrhoea in the present study was mild to moderate. The characteristic rash may, however, be associated with increased benefit from EGFR-targeted agents.[32]

The pharmacokinetics of erlotinib were similar when given as a single agent or as part of the triple-drug combination, suggesting that there was no interaction between erlotinib and capecitabine or docetaxel. Similarly, the pharmacokinetic parameters for capecitabine and its metabolites were similar whether administered with or without erlotinib. Neither of the docetaxel doses studied (60 mg/m^2 or 75 mg/m^2) appeared to affect the pharmacokinetics of erlotinib or its metabolites. While docetaxel concentrations were somewhat lower when erlotinib was co-administered, meaning that the C_{max} for docetaxel was reduced in the presence of erlotinib, there was substantial variability in the mean C_{max} for docetaxel. Consequently, the difference between the treatment groups was not considered conclusive evidence of a clinically relevant pharmacokinetic interaction (formal tests of statistical significance were not performed). Further investigations of docetaxel pharmacokinetics in combination with erlotinib and capecitabine are warranted. Nevertheless, the pharmacokinetic results indicate that exposure to the three drugs is not significantly diminished when they are given in combination.

The role of small molecule HER1/EGFR inhibitors in combination with chemotherapy is not yet fully defined. In pancreatic cancer, data from a phase III trial show that survival is modestly prolonged when erlotinib is added to gemcitabine.[15] Encouraging responses have also been reported with erlotinib in combination with chemotherapy in other tumour types, such as malignant glioma,[25] and a wide variety of advanced solid tumours.[26,28] As the first-line treatment for advanced non-small cell lung cancer, however, erlotinib added to platinum-based chemotherapy prolonged survival only in non-smokers.[33] In the present study, the response rate (67%) was encouraging for women with MBC.

In summary, the MTD of this triple-drug combination that is recommended for further study is erlotinib 100 mg/day continuously with capecitabine 825 mg/m^2 bid (days 1 to 14 of a 3-week cycle) and docetaxel 75 mg/m^2 intravenously (every 3 weeks). This regimen was generally well tolerated, with manageable skin toxicity and diarrhoea being the most commonly reported treatment-related AEs. Although pharmacokinetic interactions between erlotinib and capecitabine or docetaxel cannot be ruled out, the results provide evidence that the exposure to the three drugs is not diminished when they are given in combination. Anti-tumour activity was encouraging and further studies of this triple-drug combination in women with MBC are warranted.

Conflict of interest statement

Chris Twelves: Honoraria and advisory role payments from Roche, Merck and AstraZeneca. José Trigo: None declared. Rob Jones: Honararia from Chugai Pharmaceuticals. Flavio de Rosa: Employed by F. Hoffmann-La Roche. Ashok Rakhit: Employed by Hoffmann-La Roche Inc. Scott Fettner: Employed by Hoffmann-La Roche Inc. Tonya Wright: None declared. Jose Baselga: Honoraria from Roche, Merck, Glaxo-Smith Kline and payments for advisory roles from: Roche, AstraZeneca BMS and Merck.

Acknowledgements

The authors wish to acknowledge the invaluable contribution to the design and conduct of the study made by their collaborator, Dr. Ulrich Brennscheidt, who regrettably died before finalisation of this manuscript. We thank J. Phillipson from Gardiner-Caldwell Communications for assistance in preparation and editing, this support was funded by F. Hoffmann-La Roche.

REFERENCES

1. Chung CT, Carlson RW. Goals and objectives in the management of metastatic breast cancer. *Oncologist* 2003;**8**:514–20.
2. Hudis CA. Current status and future directions in breast cancer therapy. *Clin Breast Cancer* 2003;**4**:S70–5.
3. Baselga J, Arteaga CL. Critical update and emerging trends in epidermal growth factor receptor targeting in cancer. *J Clin Oncol* 2005;**23**:2445–59.
4. Ciardiello F, Tortora G. Anti-epidermal growth factor receptor drugs in cancer therapy. *Expert Opin Invest Drugs* 2002;**11**:755–68.
5. Salomon DS, Brandt R, Ciardiello F, Normanno N. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol* 1995;**19**:183–232.
6. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. *Nat Rev Mol Cell Biol* 2001;**2**:127–37.
7. Nicholson RI, Gee JM, Harper ME. EGFR and cancer prognosis. *Eur J Cancer* 2001;**37**:9–15.
8. Witton CJ, Reeves JR, Going JJ, Cooke TG, Bartlett JM. Expression of the HER1-4 family of receptor tyrosine kinases in breast cancer. *J Pathol* 2003;**200**:290–7.

9. Dragovich T, Huberman M, Von Hoff DD, et al. Erlotinib plus gemcitabine in patients with unresectable pancreatic cancer and other solid tumors: phase IB trial. *Cancer Chemother Pharmacol* 2007;**60**:295–303.
10. Pérez-Soler R, Chachoua A, Hammond LA, et al. Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. *J Clin Oncol* 2004;**22**:3238–47.
11. Soulières D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol* 2004;**22**:77–85.
12. Townsley CA, Major P, Siu LL, et al. Phase II study of erlotinib (OSI-774) in patients with metastatic colorectal cancer. *Br J Cancer* 2006;**94**:1136–43.
13. Winer E, Cobleigh M, Dickler M, et al. Phase II multicenter study to evaluate the efficacy and safety of Tarceva (erlotinib OSI-774) in women with previously treated locally advanced or metastatic breast cancer. *Breast Cancer Res Treat* 2002;**76**(Suppl. 1):S115 [abstract 445].
14. Trigo J, Baselga J, de Rosa F, et al. A phase IB study of TarcevaTM (erlotinib) plus capecitabine and docetaxel in metastatic breast cancer (MBC). *Clin Cancer Res* 2003;**9**(Suppl.):6096 s [abstract A74].
15. Moore M, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007;**25**:1960–6.
16. Blum JL, Jones SE, Buzdar AU, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1999;**17**:485–93.
17. Chevallier B, Fumoleau P, Kerbrat P, et al. Docetaxel is a major cytotoxic drug for the treatment of advanced breast cancer: a phase II trial of the Clinical Screening Cooperative Group of the European Organization for Research and Treatment of Cancer. *J Clin Oncol* 1995;**13**:314–22.
18. Hudis CA, Seidman AD, Crown JP, et al. Phase II and pharmacologic study of docetaxel as initial chemotherapy for metastatic breast cancer. *J Clin Oncol* 1996;**14**:58–65.
19. Ramos M, Gonzalez-Ageitos A, Amenedo M, et al. Weekly docetaxel as second-line therapy for patients with advanced breast cancer resistant to previous anthracycline treatment. *J Chemother* 2003;**15**:192–7.
20. Ravdin PM, Burris III HA, Cook G, et al. Phase II trial of docetaxel in advanced anthracycline-resistant or anthracenedione-resistant breast cancer. *J Clin Oncol* 1995;**13**:2879–85.
21. Valero V, Holmes FA, Walters RS, et al. Phase II trial of docetaxel: a new, highly effective antineoplastic agent in the management of patients with anthracycline-resistant metastatic breast cancer. *J Clin Oncol* 1995;**13**:2886–94.
22. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002;**20**: 2812–23.
23. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**:205–16.
24. Leonard R, O'Shaughnessy J, Vukelja S, et al. Detailed analysis of a randomized phase III trial: can the tolerability of capecitabine plus docetaxel be improved without compromising its survival advantage? *Ann Oncol* 2006;**17**:1379–85.
25. Prados MD, Lamborn KR, Chang S, et al. Phase 1 study of erlotinib HCl alone and combined with temozolomide in patients with stable or recurrent malignant glioma. *Neuro-oncol* 2006;**8**:67–78.
26. Jones RJ, Hanauske A, Diaz-Rubio E, et al. Final evaluation of TarcevaTM (erlotinib) in combination with FOLFOX4 in patients with solid tumors. *Clin Cancer Res* 2003;**19**(Suppl.):76 [abstract A108].
27. Mita A, Farouzesh B, Hidalgo M. Phase I, pharmacokinetic (PK), and biological studies of the epidermal growth factor receptor-tyrosine kinase (HER1/EGFR-TK) inhibitor erlotinib (OSI-774;Tarceva) in combination with docetaxel. *Eur J Cancer* 2002;**38**(Suppl. 7):S53.
28. Mita M, Patnaik A, Hammond LA, et al. Phase I, pharmacokinetic (PK) and biologic study of erlotinib (OSI-774) in combination with paclitaxel and carboplatin in advanced solid malignancies. *Proc Am Soc Clin Oncol* 2003;**22**:209 [abstract 837].
29. Ratain MJ, George CM, Janisch L, et al. Phase I trial of erlotinib (OSI-774) in combination with gemcitabine (G) and cisplatin (P) in patients with advanced solid tumors. *Proc Am Soc Clin Oncol* 2002;**21** [abstract 2115].
30. Van Cutsem E, Beale P, Delord JP, et al. Tarceva^{TM} (erlotinib) in combination with xeloda and oxaliplatin in patients with metastatic colorectal cancer (CRC) – a phase I dose escalation trial. *Clin Cancer Res* 2003;**9** [abstract A109].
31. Shepherd FA, Rodrigues PJ, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;**353**:123–32.
32. Pérez-Soler R. Can rash associated with HER1/EGFR inhibition be used as a marker of treatment outcome? *Oncology* 2003;**17**:23–8.
33. Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2005;**23**: 5892–9.