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CLINICAL TRIAL

Efficacy and safety of erlotinib in patients with locally advanced or metastatic breast cancer

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Abstract *Purpose* To evaluate the efficacy and safety of erlotinib in advanced breast cancer. *Experimental design* Multicenter, phase II study of erlotinib (150 mg orally daily). Cohort 1: progression after anthracyclines, taxanes, and capecitabine ($n = 47$). Cohort 2: progression after >1 chemotherapy for advanced-stage disease ($n = 22$). Primary endpoint was response rate (World Health Organization criteria). Secondary endpoints were safety, time to progression, and survival. *Results* One patient in each cohort ($n = 2, 3.0\%$) had a partial response. Response duration was 17 weeks for the Cohort 1 patient and 32 weeks for the Cohort 2 patient. Median time to progression was 43 days for Cohort 1 (range 1–204) and 43 days for Cohort 2 (range 25–419). Common adverse events were diarrhea, rash, dry skin, asthenia, nausea, anorexia. *Conclusion* Erlotinib had minimal activity in unselected previously treated women with advanced breast cancer. Predictive factors are needed to identify breast cancer patients who may derive benefit from erlotinib treatment.

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Introduction

Epidermal growth factor receptor (EGFR/HER1) is a member of the ErbB superfamily of type I receptor tyrosine kinases, which also includes HER2, HER3, and HER4. EGFR/HER1 is expressed in a number of epithelial tumors, and has been associated with advanced tumor stage, resistance to standard chemo- and hormone therapies, and poor patient prognosis [1]. Strategies that disrupt EGFR/HER1 signal transduction pathways are being evaluated as anti-tumor therapies and include monoclonal antibodies that bind to the extracellular domain of the receptor and low molecular weight tyrosine kinase inhibitors (TKIs) that bind to the intracellular domain.

Erlotinib is a TKI that binds competitively at the tyrosine kinase domain of EGFR/HER1 and inhibits autophosphorylation and downstream pathways that control cell proliferation and survival. Erlotinib increased response and overall survival compared with best supportive care in patients with advanced non-small cell lung cancer (NSCLC) [2], and erlotinib in combination with gemcitabine was associated with increased progression free- and overall survival versus gemcitabine alone in patients with advanced pancreatic cancer [3]. Furthermore, two anti-EGFR/HER1 monoclonal antibodies have been approved for treating patients with metastatic colorectal cancer (cetuximab and panitumumab) and advanced head and neck cancer (cetuximab) [4, 5].

In breast cancer, EGFR/HER1 expression has wide variation but has been reported in up to 91% of tumors [6], and patients with EGFR/HER1-positive tumors or tumors

that co-express EGFR/HER1 and HER2 have a worse prognosis [7, 8]. The HER2 pathway is a validated target in the treatment of breast cancer, as trastuzumab, a humanized monoclonal antibody that binds HER2, improves overall survival in women with HER2-positive early-stage and metastatic disease [9–11]. In addition, lapatinib, a dual inhibitor of EGFR/HER1 and HER2, is active in metastatic breast cancer [12, 13]. However that activity appears to be limited to patients with HER2-positive tumors. Pre-clinical studies have demonstrated that the EGFR/HER1-selective TKIs erlotinib and gefitinib inhibit breast cancer cell proliferation in vitro [14, 15], with the greatest effects in HER2-positive cell lines. However, TKIs and anti-EGFR/HER1 antibodies have not demonstrated significant activity in unselected patients with previously treated, advanced breast cancer [16–18].

The present study evaluated the efficacy, safety, and pharmacokinetics of single-agent erlotinib in patients with locally advanced or metastatic breast cancer. Pharmacokinetic results of the study have been reported elsewhere as part of a larger analysis [19] and are not presented here.

Patients and methods

Study design

This multicenter, phase II, open-label study was designed to evaluate the efficacy and safety of single-agent erlotinib in patients with locally advanced or metastatic breast cancer. The study (NCT00024219) was conducted in accordance with the U.S. Food and Drug Administration, appropriate local health authorities, and the International Conference on Harmonization E6 guidelines. The protocol, consent forms, relevant supporting information, and any advertising material were approved by the appropriate institutional review boards. All patients provided written, informed consent. Planned enrollment was up to 200 patients, and enrollment for each cohort was dependent upon the number of responses observed. For Cohort 1, four stages of enrollment were planned for up to 150 patients. Twenty-one patients were to be enrolled during the first stage. If at least one response was observed among the first 21 patients, accrual was to continue to a maximum of 50 patients during the second stage. If at least 12 responses were observed among the first 50 patients, an additional 50 patients were to be enrolled during the third stage. If at least 23 responses were observed among the first 100 patients, an additional 50 patients were to be enrolled during the fourth stage. For Cohort 2, 21 patients were initially to be enrolled. If at least one response was observed among the first 21 patients, 29 additional patients were to be enrolled, in order estimate the response rate more precisely and to collect additional safety information in that population.

Eligibility

Women ≥18 years of age were eligible for participation if they had disease progression during or after therapy with an anthracycline, a taxane, and capecitabine (Cohort 1) or disease progression during or after therapy with at least one chemotherapy regimen for locally advanced or metastatic disease (Cohort 2). Participants were required to have radiographically measurable disease ≥2 cm (≥1 cm on spiral computed tomography scan), an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, life expectancy ≥3 months, and the ability to comply with study and follow-up procedures.

Key exclusion criteria included other primary malignancies in the previous 5 years, except for adequately treated carcinoma in situ of the cervix or basal- or squamous cell skin cancer or symptomatic or untreated brain metastases; radio-, immuno-, hormone-, or chemotherapy during the 21 days prior to study onset; or prior therapy with an agent designed to target EGFR/HER1 or EGFR/HER1-specific tyrosine kinase activity.

Baseline measures

Prior to study commencement, patients underwent a complete physical examination, and a variety of baseline assessments were performed. These included radiographic evaluation of all disease sites, with up to 10 target lesions identified and followed throughout the study and ophthalmologic examination, including vital dye slit-lamp examination, corneal sensitivity test, and visual acuity test. Baseline EGFR/HER1 status was determined centrally by immunohistochemistry (IHC) (Dako; Carpinteria, CA), using a scoring system for protein overexpression similar to that used for Dako's HercepTest™ (0–1, negative; 2+, weakly positive; 3+, strongly positive). Baseline HER2 status was determined by IHC and fluorescent in situ hybridization (FISH) techniques performed at individual investigative sites (i.e., no central analysis). HER2 positivity was defined as IHC ≥2+, but confirmatory FISH testing for patients with a 2+ score was not completed in most patients. Baseline estrogen receptor (ER) and progesterone receptor (PR) status were evaluated at individual investigative sites.

Treatment

Patients began taking a daily oral dose of 150 mg erlotinib on study day 0. Treatment continued until documented disease progression (i.e., study completion) or early

termination. Patient visits occurred on day 0 and then every 2 weeks until week 8. After week 8, visits occurred every 4 weeks until week 12, after which visits occurred every 8 weeks until study completion/early termination.

Dose reduction or interruption of erlotinib treatment was allowed at any time during the study. In the event of Grade 3 or intolerable Grade 1 or 2 toxicity that was not controlled by optimal supportive care, the daily dose of erlotinib was decreased in 50 mg decrements. If erlotinib-related toxicity did not improve by at least one National Cancer Institute (NCI) Common Toxicity Criteria (CTC) [20] grade (i.e., to $\leq$2) within 2 weeks of a dose reduction, the daily dose was reduced by an additional 50 mg, until it was reduced to 25 mg, the minimum allowable study dose. Once a patient's dose was reduced, it was not re-escalated.

Efficacy

The primary efficacy outcome measure was objective response rate defined as complete or partial response sustained for $\geq$4 weeks according to World Health Organization criteria [21] assessed by the investigator. Tumors were radiographically evaluated at weeks 6 and 12 and every 8 weeks thereafter, until study completion/early termination, and progression was determined by investigator evaluation of radiographs, according to World Health Organization response criteria [21]. Patients with documented disease progression were discontinued from treatment and followed for survival every 2 months until death, loss to follow-up, or study closure.

Safety

Safety was evaluated by incidence and severity of adverse events (AEs), graded by the investigator based on NCI-CTC (version 2) guidelines; changes in laboratory parameters; changes in ophthalmologic examination results; and changes in left ventricular ejection fraction. Investigators judged whether AEs were erlotinib-related. AEs that occurred within 30 days after study completion/early termination were recorded. Patients who continued to have erlotinib-related AEs were followed monthly until the AEs resolved or were judged by the investigator to be irreversible. Cardiac ejection fraction (multiple gated acquisition scan or echocardiogram) was measured at baseline, at week 8, as clinically indicated, and at the study completion/early termination visit. Ophthalmologic evaluations were performed at baseline, as clinically indicated, and at the study completion/early termination visit.

Statistical analysis

The primary efficacy endpoint was the rate of radiologically determined objective response to single-agent erlotinib. Secondary efficacy endpoints included duration of objective response, duration of stable disease $\geq$4 months, time to disease progression, and survival. All endpoints were analyzed based on the intent-to-treat (ITT) approach of including all enrolled patients. Patients who were not evaluable for tumor response were considered nonresponders in the ITT analysis.

A 95% Blyth–Still–Casella exact confidence interval (CI) [22] was calculated for objective response rate and the proportion of patients with stable disease duration $\geq$4 months. For determining the proportion of patients with stable disease duration $\geq$4 months, patients who were not evaluable for tumor response at 4 months were considered to have experienced treatment failure in the ITT analysis. Medians and survival distribution curves for duration of response, time to disease progression, and survival were estimated using Kaplan–Meier survival analysis methods [23]. Duration of objective response was defined as the time from the initial response to first documented disease progression or death, whichever occurred first. Time to disease progression was defined as the interval from day 0 until first documented disease progression or death, whichever occurred first. Survival was defined as the interval from day 0 until death.

Missing data

Patients who discontinued the study for any reason prior to undergoing a post-baseline tumor assessment were considered nonresponders in the ITT analysis of objective response. For analyzing duration of objective response and time to disease progression, data from patients who did not experience the defined event were censored at the date of last tumor assessment. For analyzing overall survival, data from patients who had not died as of study closure were censored at the date they were last known to be alive.

Results

Patient characteristics

Sixty-nine women (Cohort 1 = 47, Cohort 2 = 22; mean age 53 $\pm$ 11.90 years, range 30–83) with histologically confirmed, locally advanced or metastatic breast cancer were enrolled between May and December of 2001 (Table 1). The majority of patients had baseline ECOG performance status of 0 or 1. The median number of prior systemic treatment regimens was 7 for Cohort 1 (range 2–20) and 6 for Cohort 2 (range 3–11) (Table 2). Approximately 40% of patients in each cohort were previously treated with trastuzumab. Three patients discontinued treatment due to adverse events, and one patient withdrew consent prior to receiving any study treatment.

Table 1 Patient baseline characteristics

Variable	Cohort 1 ($n = 47$)	Cohort 2 ($n = 22$)	Total ($n = 69$)
Age (years)			
Mean (SD)	52 (11.3)	55 (13.1)	53 (11.9)
Range	30–83	33–79	30–83
Number of prior systemic treatment regimens			
Median	7	6	6
Range	2–20	3–11	2–20
ECOG performance status			
0	20 (42.6)	12 (54.5)	32 (46.4)
1	24 (51.1)	8 (36.4)	32 (46.4)
2	2 (4.3)	2 (9.1)	4 (5.8)
Unknown	1 (2.1)	0	1 (1.4)
EGFR/HER1 (IHC) status	$n = 24$	$n = 10$	$n = 34$
0	21 (87.5)	9 (90.0)	30 (88.2)
1+	0	1 (10.0)	1 (2.9)
2+	0	0	0
3+	3 (12.5)	0	3 (8.8)
HER2 (FISH) status	$n = 5$	$n = 7$	$n = 12$
Positive	1 (20.0)	2 (28.6)	3 (25.0)
Negative	4 (80.0)	5 (71.4)	9 (75.0)
HER2 (IHC)	$n = 38$	$n = 16$	$n = 54$
Positive ($\geq$2+)	17 (44.7)	6 (37.5)	23 (42.6)
Negative	21 (55.3)	10 (62.5)	31 (57.4)
Estrogen receptor	$n = 42$	$n = 18$	$n = 60$
Positive	18 (42.8)	12 (66.7)	30 (50.0)
Negative	24 (57.1)	6 (33.3)	30 (50.0)
Progesterone receptor	$n = 40$	$n = 18$	$n = 58$
Positive	10 (25.0)	11 (61.1)	21 (36.2)
Negative	30 (75.0)	7 (38.9)	37 (63.8)
ER/PR/HER2 negative	12 (25.5)	3 (13.6)	15 (21.7)

Data are expressed as *n* (%) unless otherwise noted. HER2 positive status was defined as IHC $\geq$2+. Not all patients with a 2+ result had confirmatory FISH analysis. SD = standard deviation; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; EGFR/HER1 = epidermal growth factor receptor; ER = estrogen receptor; PR = progesterone receptor

Efficacy

There were two confirmed partial responses, one in each cohort, for a response rate of 3% (95% CI: 0.5–9.3) at the time of database lock (February 2003). The response duration was 17 weeks for the Cohort 1 patient and 32 weeks for the Cohort 2 patient. Six Cohort 1 patients and two Cohort 2 patients had a best confirmed response of stable disease, according to WHO criteria, the duration of which ranged from 10 to 15 weeks. No patients met the secondary endpoint of stable disease $\geq$4 months. Sixty (87%) of the 69 patients had progressed as of study closure. The median time to progression was 43 days for Cohort 1 (range 1–204; 95% CI: 41–46) and 43 days for Cohort 2 (range 25–419; 95% CI: 41–49). Median survival was 139 days (range 14–266) for Cohort 1 patients and 157 days (40 to 428+) for Cohort 2 patients. Thirty-four (49%) of the studied patients had died at the time of study closure (Table 3).

Safety

Sixty-eight (98%) patients who received at least one dose of erlotinib were included in the safety analysis. The patient who withdrew consent prior to receiving any study drug was not included in the safety analysis. All patients experienced at least one AE, the most common (i.e., reported by $\geq$10% of patients) of which were diarrhea, rash, dry skin, asthenia, nausea, anorexia, dry eyes, and vomiting (Table 4). Grade $\geq$3 nausea, vomiting, and diarrhea were experienced by 5.9%, 5.9%, and 4.4% of patients, respectively. Grade $\geq$2 skin rash, acne and dry skin were experience by 13.2%,

Table 2 Previous treatment and setting

Agent and setting	Cohort 1 ($n = 47$)	Cohort 2 ($n = 22$)	Total ($n = 69$)
Capecitabine	46 (97.9)	4 (18.2)[a]	50 (72.5)
Adjuvant	2 (4.3)	0	2 (2.9)
Metastatic	42 (89.4)	3 (13.6)	45 (65.2)
Taxane	46 (97.9)	22 (100)	68 (98.5)
Neo-adjuvant/adjuvant	20 (42.5)	6 (27.3)	26 (37.7)
Metastatic	29 (61.7)	18 (81.8)	47 (68.1)
Anthracycline	47 (100)	16 (72.7)	63 (91.3)
Neo-adjuvant	10 (21.3)	1 (4.5)	11 (15.9)
Adjuvant	19 (40.4)	9 (40.9)	28 (40.6)
Metastatic	22 (46.8)	9 (40.9)	31 (44.9)
Trastuzumab	18 (38.3)	9 (40.9)	27 (39.1)
Bevacizumab	4 (8.5%)	2 (9.1%)	6 (8.7%)

[a] One Cohort 2 patient received capecitabine for local/regional recurrence. Data are expressed as *n* (%)

Table 3 Best response according to World Health Organization criteria

	Cohort 1 ($n = 47$)	Cohort 2 ($n = 22$)	Total ($n = 69$)
Treated, *n* (%)	46 (97.9%)	22 (100%)	68 (98.6%)
Partial response at 6 weeks	1 (2.1%)	1 (4.5%)	2 (2.9%)
Stable disease	6 (12.8%)	2 (9.1%)	8 (11.6%)
Progressive disease	36 (76.6%)	19 (86.4%)	55 (79.7%)
Discontinued due to adverse event	5 (10.6%)	1 (4.5%)	6 (8.7%)

Table 4 Selected adverse events experienced by >10% of all patients

Event	All		Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Diarrhea	49	72.1	36	52.9	10	14.7	3	4.4	0	0
Asthenia	34	50.0	22	32.4	10	14.7	2	2.9	0	0
Acne	32	47.1	17	25.0	10	14.7	5	7.4	0	0
Nausea	28	41.2	16	23.5	8	11.8	4	5.9	0	0
Skin rash	24	35.3	15	22.1	9	13.2	0	0	0	0
Vomiting	23	33.8	14	20.6	5	7.4	4	5.9	0	0
Anorexia	19	27.9	16	23.5	3	4.4	0	0	0	0
Dry skin	18	26.5	14	20.6	4	5.9	0	0	0	0
Dry eyes	13	19.1	12	17.6	1	1.5	0	0	0	0
Dyspnea	16	23.5	8	11.8	5	7.4	2	2.9	1	1.5
Pruritis	7	10.3	4	5.9	3	4.4	0	0	0	0

22.1%, and 5.9% of patients, respectively. Two serious study drug-related AEs, as assessed by investigators, were reported: pancreatitis and fever. Three additional serious AEs in two patients (convulsion, anemia, pericardial effusion) were assessed by investigators as not related to the study drug and warranted dose interruption.

Histology

In many cases, tissue samples from original tumors were unavailable or degraded. Baseline EGFR/HER1 was assessed in samples from 34 (49.3%) patients. Three of 24 (12.5%) samples from Cohort 1 were classified as EGFR/HER1-positive (3+), and one of 10 (10%) samples from Cohort 2 was classified as EGFR/HER1-positive (1+), according to IHC. Eighty-eight percent of the samples were EGFR/HER1 negative. Baseline HER2 was assessed in 54 samples. Seventeen of 38 (44.7%) samples from Cohort 1 were determined to be HER2 positive by IHC (defined as ≥2+), and 6 of 16 (37.5%) samples from Cohort 2 were HER2 positive by IHC. The HER2 FISH results are summarized in Table 2. It is important to note that HER2 positive status was defined as IHC ≥2+, and confirmatory FISH testing for patients with a 2+ score was not completed in most patients. Fifteen (21.7%) patients had tumors that were ER/PR/HER2 negative (i.e., triple negative) (Table 1). Of the two patients who demonstrated a partial response, the tissue sample from the Cohort 1 patient was triple negative, and the tissue sample from the Cohort 2 patient was ER and PR negative and HER2 positive.

Discussion

Erlotinib had minimal activity in unselected previously treated women with locally advanced or metastatic breast cancer. Two patients had a partial response, and eight patients had stable disease as their best response to erlotinib therapy, the duration of which ranged from 10 to 15 weeks. The incidence of AEs and overall safety in the present patient population were comparable to that observed in previous evaluations of erlotinib [2, 3, 24–26] and other EGFR/HER1 tyrosine kinase inhibitors [27]. The majority of AEs were related to skin and gastrointestinal toxicity and were believed to result from anti-EGFR/HER1 activity in normal EGFR/HER1-expressing tissue [27]. No new drug-related safety issues were identified.

The low response rate we observed adds to a growing body of evidence that single-agent anti-EGFR/HER1 therapies have limited efficacy in unselected previously treated breast cancer patients [16, 18, 28]. A possible reason for the lack of a significant erlotinib effect is that the study population was selected only for disease progression and prior treatment rather than for specific tumor profiles. Unlike HER2-positivity, which predicts response to trastuzumab [9–11] and lapatinib [12], and ER and PR positivity, which predicts response to tamoxifen and aromatase inhibitors,

biological markers that predict response to anti-EGFR/HER1 agents have not been identified in breast cancer. This is not the case for all tumor types. For instance, in-frame deletions in exon 19, single missense mutations in exon 21, and in-frame duplications/insertions in exon 20 of the EGFR/HER1 tyrosine kinase domain appear to be associated with response to erlotinib and gefitinib in NSCLC [29, 30]. On the other hand, mutations in the KRAS gene, a downstream effector of EGFR/HER1 activation, have been associated with a lack of response to anti-EGFR/HER1 therapy in NSCLC [30]. KRAS mutations have also been associated with resistance to the anti-EGFR/HER1 antibodies cetuximab and panitumumab in colorectal cancer [31–34], while high levels of the EGFR/HER1 ligands epiregulin and amphiregulin were associated with response to cetuximab [32]. Activating mutations in EGFR/HER1 have not been identified in breast cancer, and KRAS mutations occur in only 5% of tumors [35].

Several attempts have been made to identify a subgroup of patients responsive to anti-EGFR/HER1 therapy in breast cancer. A recent study reported that short-term, preoperative erlotinib therapy in women with untreated breast cancer inhibited Ki67, a molecular marker of cell proliferation, in ER-positive, but not HER2-positive or triple-negative tumors. In another study, preoperative treatment with gefitinib alone or combined with the aromatase inhibitor anastrozole was associated with Ki67 reduction in ER- and EGFR/HER1-positive primary breast cancer [36]. In a phase 2 study of patients with pretreated triple-negative tumors, single-agent cetuximab had modest activity, with 2 of 31 (6%) patients experiencing a partial response and 10% of patients having responsive or stable disease for $\geq$24 weeks [28]. In patients with HER2-positive tumors, gefitinib plus trastuzumab did not increase antitumor activity, despite evidence of preclinical synergy of anti-EGFR/HER1 and anti-HER2 therapy [37]. Similarly, preoperative gefitinib plus anastrozole did not increase clinical response or decrease tumor cell proliferation compared with anastrozole alone in patients with ER-positive tumors, although preclinical models suggested that anti-EGFR/HER1 therapy reversed resistance to endocrine therapy [38]. Taken together, those results suggest that anti-EGFR/HER1 agents are unlikely to have clinical activity in HER2-positive or triple-negative breast cancers. This is contrary to the results of preclinical studies suggesting that proliferation of triple negative tumors is EGFR/HER1 dependent, and demonstrates that preclinical models are not always consistent with clinical findings.

Although anti-EGFR/HER1 agents have been shown to inhibit EGFR/HER1 phosphorylation and EGFR/HER1-dependent processes in breast cancer cell lines and biopsy tissue [17, 39, 40], inhibition does not always correlate with anti-tumor effects. This suggests that tumor proliferation may be under the control of alternate growth factor pathways in the presence of EGFR/HER1 inhibitors [41] and the anti-tumor activity of anti-EGFR/HER1 agents may be improved by combining them with therapies that target other signal transduction pathways. To that end, preliminary efficacy results of ongoing studies of cetuximab plus carboplatin, a platinum-based chemotherapy, in the triple negative population are promising.

In conclusion, single-agent erlotinib was well-tolerated but had minimal activity in unselected, previously treated women with locally advanced or metastatic breast cancer. Predictive factors are needed to identify breast cancer patients who may derive the greatest benefit from erlotinib treatment, either alone or in combination with other therapies.

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