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A Multicenter Phase II Study of Erlotinib and Sorafenib in Chemotherapy-Naïve Patients with Advanced Non–Small Cell Lung Cancer

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Abstract

Purpose: This multicenter, phase II study evaluates the efficacy and safety of erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, plus sorafenib, a multityrosine kinase inhibitor against vascular endothelial growth factor receptors, in patients with previously untreated advanced non–small cell lung cancer (NSCLC).

Experimental Design: Chemotherapy-naïve patients with stage IIIB/IV NSCLC received erlotinib (150 mg once a day) and sorafenib (400 mg twice a day) until disease progression or unacceptable toxicity. The primary end point was the rate of nonprogression at 6 weeks. Secondary end points included objective response rate (ORR), time to progression, overall survival, and adverse events. Exploratory end points included pretreatment *EGFR* and *KRAS* mutation status, pharmacokinetics, and cytochrome P450 polymorphisms.

Results: Fifty patients initiated therapy. The nonprogression rate at 6 weeks was 74%: 12 (24%) partial response and 25 (50%) stable disease. Ultimately, the ORR was 28%. Median time to progression was 5.0 months [95% confidence interval (95% CI), 3.2-6.8 months]. Median overall survival was 10.9 months (95% CI, 3.8-18.1 months). Grade 3/4 adverse events included fatigue (16%), hand-foot skin reaction (16%), rash (16%), diarrhea (14%), and hypophosphatemia (42%). There was one treatment-related fatal pulmonary hemorrhage. Patients with wild-type *EGFR* had a higher ORR (19%) than previously reported for single-agent erlotinib/sorafenib. Erlotinib levels were lowered. This was associated with CYP3A4 polymorphism and was possibly due to sorafenib.

Conclusion: Despite a possible drug interaction, sorafenib plus erlotinib has promising clinical activity in patients with stage IIIB/IV NSCLC and has an acceptable safety profile. Further evaluation of this combination as potential salvage therapy in *EGFR* mutation–negative patients and the possible drug interaction is warranted. *Clin Cancer Res; 16(11); 3078–87. ©2010 AACR.*

There is an interplay between the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) pathways, with preclinical and early clinical studies demonstrating an additive antitumor effect after their simultaneous inhibition (1). Early clinical trials combining two anti-EGFR/VEGF agents with established clinical activity, erlotinib and bevacizumab, reported encouraging although modest results in non–small cell lung cancer (NSCLC; refs. 2, 3). However, disappointingly, a recent phase III trial (BeTa) failed to show a survival difference when bevacizumab was added to erlotinib compared with erlotinib alone as a second-line treatment. This was despite a doubling of both progression-free survival and response rate (4). Newer oral VEGF receptor (VEGFR) tyrosine kinase inhibitors may improve outcomes. Sorafenib is an oral multikinase inhibitor against VEGFR-1, VEGFR-2, and VEGFR-3; the RAF/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase pathway; platelet derived growth factor receptors α and β; RET; c-Kit; and Flt-3. It inhibits tumor cell proliferation and angiogenesis (5). Recent clinical data show efficacy of sorafenib monotherapy in NSCLC (6–8). In addition, a phase I study established the safety and tolerability of

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Translational Relevance

Targeted therapies are increasingly being investigated as new treatment options in oncology. This is the first phase II clinical trial in which erlotinib (an epidermal growth factor receptor inhibitor) and sorafenib (a multikinase tyrosine inhibitor) are combined as a first-line treatment for stage IIIB/IV non–small cell lung cancer (NSCLC). The clinical activity shown is comparable with that obtained with standard chemotherapy regimens in the first-line setting. Although patients with activating *EGFR* mutations had higher response rates, the results do not seem superior than with EGFR tyrosine kinase inhibitor monotherapy. In contrast, in *EGFR* mutation–negative patients, the study combination achieved higher response rates than those reported with either agent as monotherapy. Further evaluation of this combination as a new salvage therapy option for *EGFR* mutation–negative NSCLC is warranted.

combining sorafenib and erlotinib with promising antitumor activity for solid tumors, whereas preclinical data show synergism even in EGFR inhibitor–resistant NSCLC (9, 10).

This multicenter, single-arm, prospective phase II study evaluates the clinical activity and safety of sorafenib combined with erlotinib in chemotherapy-naïve patients with advanced NSCLC. Enrollment was irrespective of histologic subtype, as there were no safety concerns for sorafenib in squamous cell (SCC) patients at the time. In addition, pretreatment *EGFR* and *KRAS* mutation status, erlotinib and sorafenib pharmacokinetics, and cytochrome P450 (CYP) polymorphisms were investigated.

Materials and Methods

Patient selection

Patients with pathologically documented, inoperable, locally advanced, recurrent, or metastatic (stage IIIB or IV) NSCLC were eligible for enrollment. Other inclusion criteria were age ≥18 years; Eastern Cooperative Oncology Group performance status 0 or 1; estimated life expectancy ≥12 weeks; presence of ≥1 measurable lesion according to Response Evaluation Criteria of Solid Tumors (RECIST; ref. 11); and adequate hematologic, renal, and hepatic function. Patients with prior exposure to chemotherapy or EGFR-directed agents were excluded. Other exclusion criteria included symptomatic brain metastases (unless >1 month from radiotherapy and off steroids), severe or unstable systemic disease, seizure disorder requiring medication (steroids or antiepileptics), history of bleeding diathesis or cardiac disease, and uncontrolled hypertension. All patients provided written informed consent.

Study design and treatment

Sorafenib, 400 mg twice a day, and erlotinib, 150 mg once a day, were orally self-administered. Patients were instructed to take their medication at the same time each day. Erlotinib was taken at least 1 hour before or 2 hours after the ingestion of food or other medication. A missed dose was not subsequently taken. Patients were instructed to notify study site personnel of missed doses and completed a medication diary in the first 6 weeks of treatment. Patient adherence to sorafenib was further assessed by a health professional–recorded dispensing log throughout the treatment duration. Treatment continued until disease progression, intolerable toxicity, or withdrawal of consent. On progression, patients could receive second-line chemotherapy. When required, based on individual patient tolerability, dose reductions (to 100 or 50 mg/d for erlotinib and 400 mg/d for sorafenib) and treatment interruptions (maximum 2 weeks) could take place at any time during the study. Concomitant CYP3A4 modulator drugs were avoided where possible, and patients were advised not to ingest grapefruit juice.

Approval was obtained from the ethics committees of the three participating centers. The study adhered to the principles of the Declaration of Helsinki and ICH/Good Clinical Practice guidelines.

Study assessments

The primary end point was nonprogression rate (NPR) at 6 weeks; that is, the number of subjects without progression according to RECIST at 6 weeks after the start of treatment. A recently published landmark survival analysis of ~1,000 patients from three randomized Southwest Oncology Group (SWOG) trials of platinum-based chemotherapy concluded that disease control rate (equivalent to NPR) at week 8 is a more powerful predictor of survival than is traditional tumor response rate in advanced NSCLC (12). Secondary end points included objective response rate (ORR; according to RECIST), time to disease progression (TTP; time from start of treatment to documented progression of disease), overall survival (OS; time from start of treatment to death, irrespective of cause), and safety. Contrast-enhanced computed tomography (CT) scans of the thorax were done every 6 weeks for tumor response assessment. Clinical assessment and laboratory tests (urinalysis, hematology, coagulation, thyroid function, and blood chemistry) were done every 3 weeks in the first 3 months, then every 6 weeks and 28 days after the last dose of erlotinib and sorafenib. All adverse events were reported, and severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

Exploratory assessments

EGFR *and* KRAS *mutation analysis.* Pretreatment tumor specimens were collected. In those with sufficient tissue for direct DNA sequencing, tumor cells were isolated by manual dissection of 10-μm-thick formalin-fixed

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paraffin-embedded sections. All DNA isolates were subjected to high-resolution melting analysis for exons 19 through 21 of the *EGFR* gene and exons 1 and 2 of the *KRAS* gene, as previously described (13, 14). If an aberrant melting-out pattern was identified, direct sequencing of the high-resolution melting PCR products was done to determine the specific sequence alteration. The percentage of tumor cells was ≥5% in all samples; that is, above the analytic sensitivity of the high-resolution melting assay.

Pharmacokinetics. Plasma concentrations of erlotinib and sorafenib were quantified from plasma samples collected on days (D) 7 and 21 of treatment using a validated liquid chromatography/tandem mass spectrometry assay (15). Chromatography was conducted using a Dionex Ultimate 3000 system coupled with an Applied Biosciences SCIEX API 3000 mass spectrometer for detection. Data acquisition and integration were carried out with the software Analyst version 1.42 (Applied Biosciences) in combination with Dionex chromeleon LC modules, version 6.8, controlled by Dionex Mass link version 2.0 software.

CYP polymorphism. CYP genotyping was done by examining the melting curves from real-time PCR fluorescence resonance energy transfer assays for CYP3A4 and CYP3A5 as previously described (16, 17).

Statistical methods

To be able to discontinue the trial early if the study drug combination showed insufficient activity, a two-stage Simon's optimal design ($p_0 = 0.40$, $p_1 = 0.60$, $\alpha = 0.05$, $\beta = 0.20$) was used (18). If ≥9 of the first 16 patients (stage 1) had progressed within 6 weeks, the study would discontinue and the treatment would be declared to have insufficient activity. Otherwise, a further 30 patients would be required in stage 2. Taking into account an estimated loss to follow-up of 5%, the planned sample size was 48 patients. The optimal benchmark for NPR is unknown. In view of the 62% disease control rate at week 8 in the three phase III SWOG trials, we chose a NPR at week 6 of ≥50% as our benchmark; that is, the study drug combination would be of interest for further investigation if 50% patients were "nonprogressive" at 6 weeks. An identical approach was taken by Giaccone et al. in their study evaluating the clinical efficacy of single-agent erlotinib in first-line treatment of unselected patients with advanced NSCLC (19). We acknowledge that further clinical evaluation and experience with this new end point is needed to establish this benchmark.

Efficacy and safety analysis included all patients who received ≥1 dose of erlotinib and/or sorafenib. TTP and OS are summarized using the Kaplan-Meier method with median event time and a two-sided 95% confidence interval (95% CI) for the median provided for each end point. Fisher's exact and log-rank statistics tested associations with tumor response and TTP or OS for significance. Drug levels on D7 and D21 were compared using the Wilcoxon signed-rank test and related to CYP polymorphism, clinical characteristics, and concurrent medication (proton pump inhibitors, H_2-antagonists, dexamethasone, and CYP3A4 modulators) using the Mann-Whitney test. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Patients

Between December 2007 and October 2008, 50 patients were enrolled and started treatment. Baseline characteristics are depicted in Table 1. At the time of this analysis, median follow-up is 10.4 months (range 0.7-21.3 months) and the median number of cycles is 2.7 (range 0.4-13.7). Six patients (12%) remain on treatment. Treatment discontinuation was due to progression of disease in 30 patients, adverse events in 8 patients, 4 deaths (1 treatment related, 1 due to progression of disease, and 2 from other causes), and 1 withdrawal of consent, whereas 1 patient was lost to follow-up.

Tumor response

Twelve (75%) of the first 16 patients (stage 1) had not progressed at 6 weeks; hence, the second stage of the study was completed. The NPR at week 6 was 74%: 12 patients (24%) had partial response and 25 (50%) had stable disease. Ultimately, 14 patients achieved partial response, of which 11 were confirmed by a repeat CT scan ≥6 weeks later, giving an ORR of 28%. Of the 3 patients with unconfirmed partial response, 1 was lost to follow-up and the other 2 discontinued study medication before the next follow-up CT scan due to toxicity. Twenty-three patients (46%) had stable disease and 8 (16%) had progressive disease as their best clinical response (Table 2). Five patients were not evaluable for response: 4 discontinued treatment before the week 6 CT scan (1 postoperative death, 1 grade 3 fatigue, 1 withdrawal of consent, and 1 fatal hemoptysis), and 1 patient developed a large cavity in the primary tumor superimposed by infection. Eighteen patients (36%) developed tumor cavitation during the course of treatment. There were no tumor cavitations at baseline. Incorporating cavitations into response assessment as proposed by Crabb et al. (20) reclassified four stable diseases as partial response, increasing the ORR to 36%.

TTP and survival

At the time of analysis, 21 patients remain alive, of whom 6 are progression-free on therapy. Median TTP is 5.0 months (95% CI, 3.2-6.8 months). Median survival is 10.9 months (95% CI, 3.8-18.1 months; Table 2). Twenty-two of 44 patients who discontinued study treatment received second-line platinum-based chemotherapy. Their survival is significantly longer than those who did not receive chemotherapy [median 12.5 months (95% CI, 11.6-13.3) versus 3.6 months (95% CI, 1.9-5.4), $P = 0.007$]. Patients with adenocarcinoma ($n = 36$) had a longer TTP and OS compared with patients with nonadenocarcinoma ($n = 14$) histology [5.5 months (95% CI,

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Table 1. Baseline patient demographics and characteristics

Characteristic	Sorafenib and erlotinib (*N* = 50) No. of patients (%)
Sex	
Female	22 (44)
Male	28 (56)
Age, y	
Median	60
Range	41-78
Ethnicity	
Caucasian	45 (90)
Black	2 (4)
Asian	3 (6)
ECOG PS	
0	30 (60)
1	20 (40)
Smoking history	
Current	16 (32)
Previous	23 (46)
Never*	11 (22)
Tumor histology	
Adenocarcinoma	36 (72)
Squamous	5 (10)
Large cell	6 (12)
NSCLC NOS	3 (6)
Tumor stage	
IIIB	13 (26)
IV	37 (74)
EGFR mutation†	
Negative	31 (62)
Positive	7 (14)
Unknown	12 (24)
KRAS mutation‡	
Negative	33 (66)
Positive	5 (10)
Unknown	12 (24)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; BAC, bronchioloalveolar carcinoma; NOS, not otherwise specified.
*Less than 100 cigarettes in a lifetime.
†Deletion in exon 19 or L858R in exon 21.
‡Mutation in codon 12 or codon 13.

3.5-7.4) versus 3.0 months (95% CI, 0.7-5.2), $P = 0.03$, and 12.5 months (95% CI,10.1-14.8) versus 4.7 months (95% CI,0.9-8.5), $P = 0.02$]. SCC ($n = 5$) tended toward a shorter OS compared with nonsquamous ($n = 45$) histology [2.0 months (95% CI,1.1-2.8) versus 12.4 months (95% CI, 8.4-16.4), $P = 0.06$]. Patients who developed tumor cavitations tended toward a longer TTP [5.9 months (95% CI, 5.3-6.5) versus 3.8 months (95% CI,1.8-5.8), $P = 0.13$] and OS [13.7 months (95% CI, —] versus 5.8 months (95% CI, 2.9-8.7), $P = 0.13$].

Safety and tolerability

Most adverse events were mild to moderate in severity and did not interfere with scheduled treatment. The most commonly reported adverse events are shown in Table 3. Grade 3/4 adverse events include fatigue (16%), hand-foot skin reaction (16%), rash (16%), diarrhea (14%), and hypophosphatemia (42%). Seven patients (14%) had an adverse event–related transient dose interruption, and 15 patients (30%) underwent a dose reduction: 8 patients for erlotinib, 3 for sorafenib, and 4 for both erlotinib and sorafenib. All dose reductions and interruptions occurred later than week 3. Eight patients (16%) permanently discontinued therapy because of adverse events. Four deaths occurred during study conduct. One was possibly treatment related; a 67-year-old Caucasian male with stage IV SCC developed fatal pulmonary hemorrhage 35 days after starting treatment.

Exploratory end points

EGFR *and* KRAS *mutation analysis.* Tumor samples from 38 patients (76%) were successfully analyzed for *EGFR* and *KRAS* mutations. Seven patients had an activating *EGFR* mutation (five exon 19 deletions and two exon 21 L858R point mutations) and five had a *KRAS* mutation (all in codon 12 of exon 1). Five (71%) of the *EGFR* mutation–positive patients achieved a partial response versus six (19%) of the mutation–negative patients ($P = 0.01$; Table 4). The remaining *EGFR* mutation–positive patients achieved stable disease, giving a disease control rate of 100% compared with 71% in mutation-negative patients ($P = 0.16$). TTP was longer in *EGFR* mutation–positive compared with *EGFR*-negative patients, although this was not statistically significant. The median OS of *EGFR* mutation–positive patients has not yet been reached (Table 4; Fig. 1). In the five patients with a known *KRAS* mutation, three had stable disease (ranging from 2.3 to 4.3 months), one withdrew consent before response evaluation, and one developed a large cavity in the primary tumor with superimposed infection. Patients with a *KRAS*

Table 2. Summary of clinical efficacy

Assessment	Sorafenib and erlotinib (*N* = 50) No. of patients (%)
NPR at 6 wk	37 (74)
Objective response	
Complete response	0 (0)
Partial response	14 (28)
Stable disease	23 (46)
Progressive disease	8 (16)
Not evaluable	5 (10)
Median TTP, mo	5.0
95% CI	3.2-6.8
Median survival, mo	10.9
95% CI	3.8-18.1

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Table 3. Nonhematologic treatment–related adverse events reported by at least 10% patients

Category	Adverse event	All grades *n* (%)	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)
Cardiac	Hypertension	5 (10)	2 (4)	2 (4)	1 (2)	0 (0)
Constitutional	Fatigue	27 (54)	9 (18)	10 (20)	8 (16)	0 (0)
	Fever—no infection	5 (10)	4 (8)	1 (2)	0 (0)	0 (0)
	Rigors/chills	7 (14)	7 (14)	(0)	0 (0)	0 (0)
	Weight loss	10 (20)	2 (4)	8 (16)	0 (0)	0 (0)
Dermatology	Acneiform rash	23 (46)	10 (20)	10 (20)	3 (6)	0 (0)
	Alopecia	11 (22)	9 (18)	2 (4)	0 (0)	0 (0)
	Dry skin	8 (16)	8 (16)	0 (0)	0 (0)	0 (0)
	Hand-foot skin reaction	30 (60)	9 (18)	13 (26)	8 (16)	0 (0)
	Rash/desquamation erythema	14 (28)	4 (8)	5 (10)	4 (8)	1 (2)
Endocrine	Hypothyroidism (TSH >5.0 mU/L)	11 (22)	7 (14)	4 (8)	0 (0)	0 (0)
	High PTH (>11 pmol/L)	13 (26)	13 (26)	0 (0)	0 (0)	0 (0)
Gastrointestinal	Anorexia	17 (34)	9 (18)	6 (12)	2 (4)	0 (0)
	Constipation	8 (16)	8 (16)	(0)	0 (0)	0 (0)
	Diarrhea	42 (84)	21 (42)	14 (28)	7 (14)	0 (0)
	Dry mouth syndrome	12 (24)	10 (20)	2 (4)	0 (0)	0 (0)
	Nausea	21 (42)	14 (28)	6 (12)	1 (2)	0 (0)
	Mucositis/stomatitis-oral cavity	14 (28)	8 (16)	4 (8)	2 (4)	0 (0)
	Taste alteration/dysgeusia	13 (26)	11 (22)	2 (4)	0 (0)	0 (0)
	Vomiting	12 (24)	7 (14)	4 (8)	1 (2)	0 (0)
Hemorrhage	Nose	7 (14)	6 (12)	1 (2)	0 (0)	0 (0)
Ocular	Dry eye syndrome	6 (12)	6 (12)	0 (0)	0 (0)	0 (0)
Pain	Headache	8 (16)	2 (4)	6 (12)	0 (0)	0 (0)
Pulmonary	Cough	13 (26)	8 (16)	5 (10)	0 (0)	0 (0)
	Dyspnea	6 (12)	5 (10)	0 (0)	1 (2)	0 (0)
	Voice change/hoarseness	15 (30)	15 (30)	0 (0)	0 (0)	0 (0)

Abbreviations: TSH, thyroid-stimulating hormone; PTH, parathyroid hormone.

mutation had a shorter TTP and OS compared with wild-type patients, although this was not statistically significant (Table 4).

Pharmacokinetics. Steady-state plasma erlotinib and sorafenib concentrations, determined in 47 patients on D7 and 42 patients on D21, showed considerable interpatient variability. Sorafenib levels were lower than those previously reported for monotherapy but remained stable [mean 1.79 μmol/L (SD ± 0.96) on D7 and mean 2.14 μmol/L (SD ± 0.95) on D21, $P = 0.12$; Fig. 2B; refs. 21, 22]. Erlotinib levels were below the previously reported therapeutic level of 1.27 μmol/L in all patients on D7 and

Table 4. Clinical efficacy by *EGFR* and *KRAS* mutation status

	EGFR mutation			*KRAS* mutation		
	Positive (*n* = 7) *n* (%)	Negative (*n* = 31) *n* (%)	*P*	Positive (*n* = 5) *n* (%)	Negative (*n* = 33) *n* (%)	*P*
Best objective response						
Partial response	5 (71)	6 (19)	0.01	0 (0)	11 (33)	
Stable disease	5 (29)	16 (52)		3 (60)	14 (42)	
Progressive disease	0 (0)	4 (13)		0 (0)	5 (15)	
Not assessable	0 (0)	5 (16)		2 (40)	3 (9)	
Median TTP, mo	6.9	5.0	0.30	3.8	5.6	0.39
95% CI	4.1-9.6	3.4-6.6		—	4.3-6.7	
Median survival, mo	Not reached	6.3	0.26	4.7	12.4	0.17
95% CI		0.5-12.2		0-9.8	4.7-20.2	

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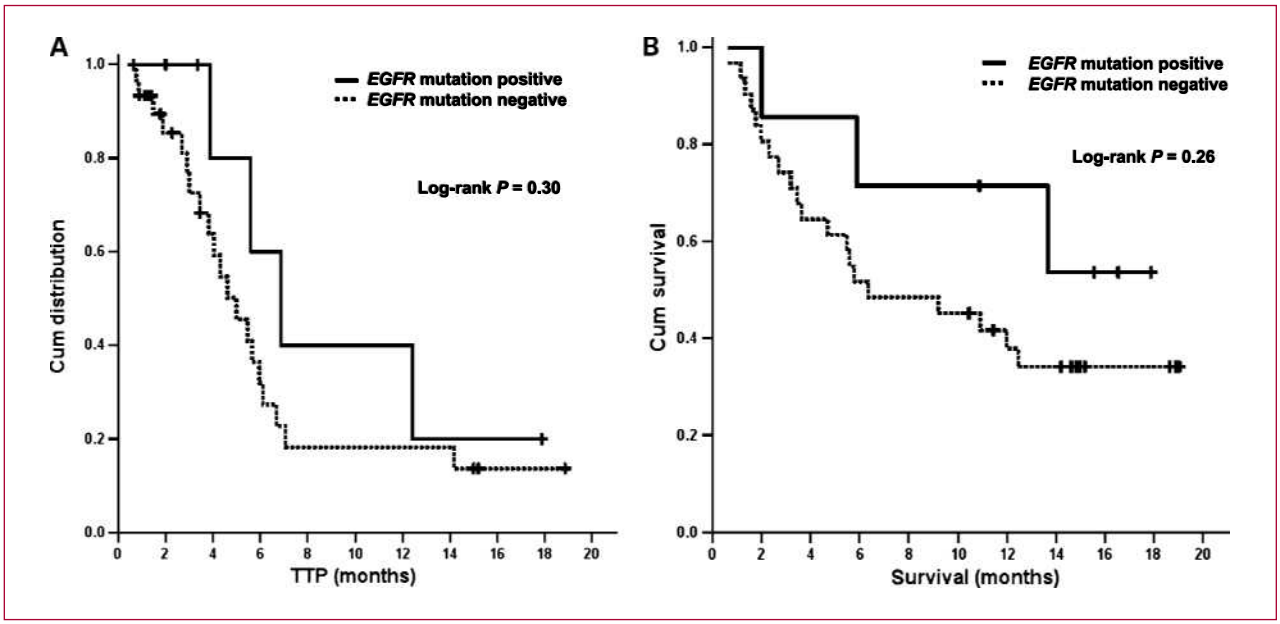

Fig. 1. Time to progression (A) and survival curves (B) for *EGFR* mutant and *EGFR* mutation–negative patients. Bars indicate censored patients at the cutoff point.

D21. Mean erlotinib concentration on D7 was 0.35 μmol/L (SD ± 0.22) and decreased to 0.25 μmol/L (SD ± 0.23) on D21 (P = 0.05), with males showing a decrease more frequently than females (P = 0.03; Fig. 2A). Six patients were taking concomitant dexamethasone, 15 patients a proton pump inhibitor, and 1 patient a weak CYP3A4 inhibitor (mirtazapine). Mean sorafenib levels were lower in patients receiving a proton pump inhibitor compared with those who were not, on both D7 [1.33 μmol/L (SD ± 0.57) versus 2.00 μmol/L (SD ± 1.03), P = 0.02] and D21 [1.49 μmol/L (SD ± 0.94) versus 2.43 μmol/L (SD ± 0.81), P = 0.003]. Erlotinib levels did not correlate with proton pump inhibitor use, and drug levels were not statistically related to smoking status. Patients with erlotinib plasma levels less than the median on D21 had a shorter TTP than those with levels greater than the median [4.3 months (95% CI, 1.9-6.7) versus 5.5 months (95% CI, 3.9-7.1), P = 0.04]. Patients with a decrease between D7 and D21 showed a trend toward a shorter survival (P = 0.07).

Regarding toxicity, patients with sorafenib plasma levels greater than median at D21 were more likely to develop grade 2 to 3 diarrhea than those with levels less than median (P = 0.04). There was no significant relation with hand-foot skin reaction or rash.

CYP polymorphisms. CYP3A4 and CYP3A5 genotyping was done in 41 patients. Thirty-four patients were CYP3A4 *1A/*1A homozygotes (wild-type), 6 patients were CYP3A4 *1A/*1B heterozygotes, and 1 patient was a CYP3A4 *1B/*1B variant homozygote. Thirty-one patients had CYP3A5 *3/*3 genotype, eight CYP3A5 *1/*3, and two CYP3A5 *1/*1. Patients with wild-type CYP3A4 had higher plasma erlotinib levels than patients with CYP3A4 polymorphism (CYP3A4 *1A/*1B or *1B/*1B) on D7 [mean 0.36 μmol/L (SD ± 0.22) versus mean 0.18 (SD ± 0.22), P = 0.02] and D21 [mean 0.29 μmol/L (SD ± 0.24) versus 0.12 (SD ± 0.22), P = 0.06; Fig. 2C]. They also tended toward higher sorafenib levels on D21 [2.28 μmol/L (SD ± 0.88) versus 1.55 μmol/L (SD ± 0.91), P = 0.07; Fig. 2D]. CYP3A5 genotype was not related to erlotinib or sorafenib levels.

Discussion

The VEGF and EGFR pathways play an important role in NSCLC. In the present study, the combination of sorafenib and erlotinib showed promising antitumor activity with a NPR at 6 weeks of 74% and an ORR of 28%. Furthermore, the TTP of 5 months and median survival of 11 months are comparable with those obtained with standard first-line chemotherapy regimens, warranting further study of this drug combination.

The activity of this combination was likely underestimated by the standard RECIST criteria. Tumor cavitation frequently develops during antiangiogenic treatment, sometimes with little or no change, or even an increase, in tumor diameter (23). In the present study, 18 patients (36%) developed cavitations. Recently, Crabb et al. proposed an alternate response assessment for angiogenesis inhibitors in which the longest diameter of a cavity (zero if no cavity present) is subtracted from the longest diameter of the lesion to provide an alternate measurement of the target lesion (20). Applying this method to our study, four stable diseases were reclassified as partial response, increasing the ORR from 28% to 36%. RECIST is also likely to underestimate activity in other trials, and the

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application of this new response assessment tool would thus similarly increase reported response rates, particularly in trials studying antiangiogenic agents. In our study, patients who developed tumor cavitations tended toward a longer TTP than patients who did not, suggesting that cavitation may be an (early) reflection of treatment efficacy.

Recently, the phase III ESCAPE trial (carboplatin/paclitaxel with versus without sorafenib) was stopped early after a planned interim analysis concluded that the study would not meet its primary end point of improved OS and reported a higher mortality in patients with SCC receiving sorafenib compared with placebo (24). Consequently, the phase III NExUS trial (gemcitabine/cisplatin with versus without sorafenib) is now excluding patients with SCC. In our study, SCC was associated with a trend toward a shorter survival, and the only treatment-related death (fatal pulmonary hemorrhage) occurred in SCC. We therefore recommend that, until more safety data is available from ongoing trials, patients with SCC be excluded from subsequent clinical trials of sorafenib.

Activating mutations in the *EGFR* gene are associated with response to EGFR inhibitors. These mutations are reported in ~10% of patients in the West. The higher percentage (18%) of *EGFR* mutation–positive patients in our study reflects the referral pattern of patients to our tertiary centers from other hospitals. The phase III Iressa Pan-Asia Study (IPASS) reports an ORR of 71% and prolonged progression-free survival in *EGFR* mutation–positive patients treated with gefitinib compared with carboplatin/paclitaxel as first-line treatment (25). In contrast, *EGFR* mutation–negative patients had an ORR of 1.1% when treated with gefitinib and benefited more from chemotherapy. Our study completed enrollment before the IPASS results were reported. We similarly found a higher ORR (71% versus 19%) and disease control rate (100% versus 71%) and a trend toward a longer TTP in *EGFR* mutation–positive patients. The median OS of these patients has not yet been reached. Although only five patients had an activating *EGFR* mutation and the results may thus be limited by the small sample size, our data do not suggest that the combination of sorafenib and erlotinib is superior to EGFR tyrosine kinase inhibitor monotherapy as first-line treatment in *EGFR* mutation–positive patients and thus do not support further study of the combination in this setting.

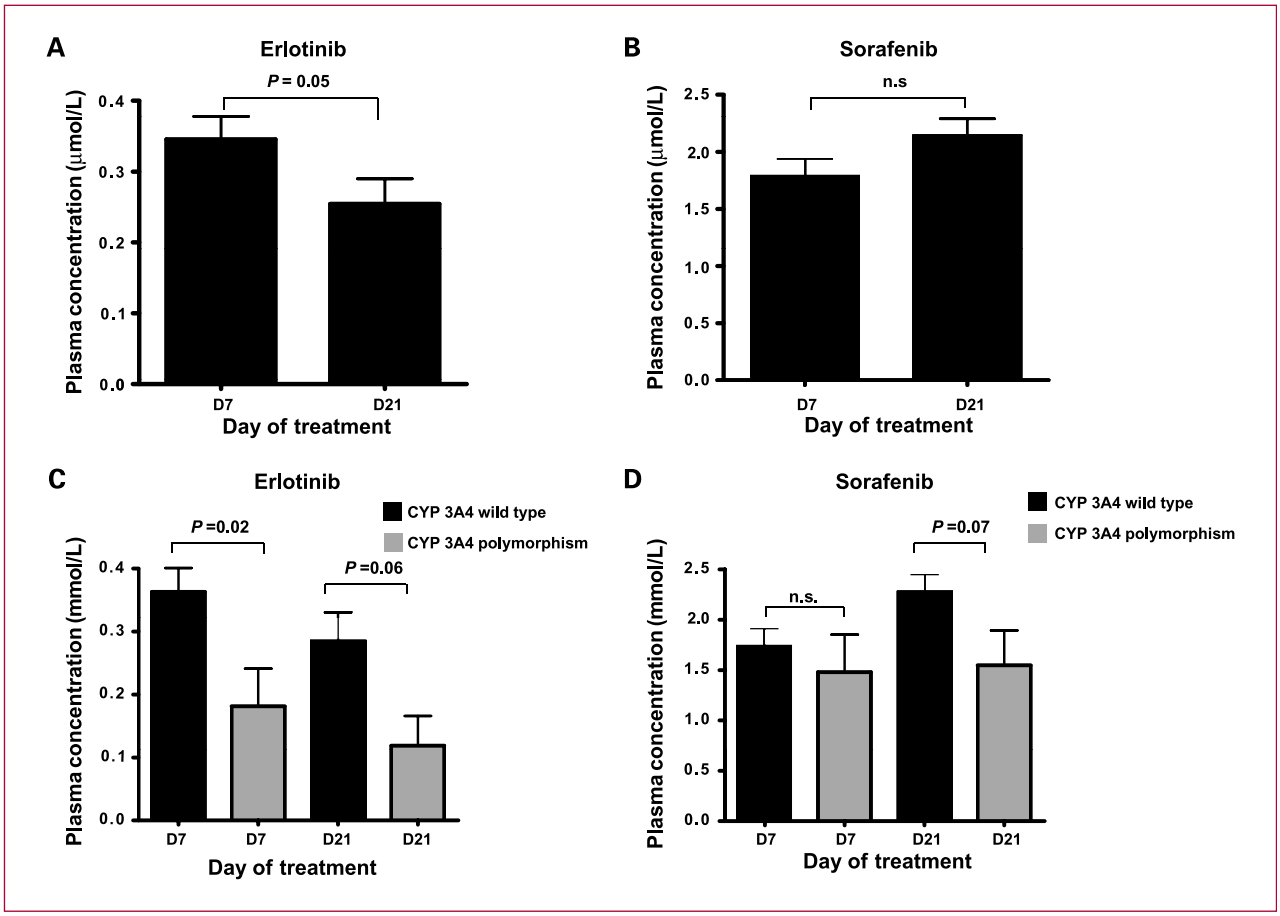

Fig. 2. Erlotinib (A) and sorafenib (B) plasma concentration after 7 (D7) and 21 (D21) days of treatment. C, erlotinib plasma concentration according to CYP3A4 polymorphism.

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The clinical outcome of *EGFR* mutation–negative patients in our study is insufficient to merit further study of sorafenib plus erlotinib in the first-line setting in this subgroup of patients. However, the ORR of 19% is higher than the very low response rates reported in *EGFR* mutation–negative patients treated with EGFR tyrosine kinase inhibitor monotherapy in the IPASS study and other trials. This suggests that the combination may be an effective salvage therapy option in patients with wild-type *EGFR*. Recently, Spigel et al. completed enrollment of a randomized phase II trial comparing erlotinib and sorafenib with erlotinib alone in relapsed unselected NSCLC patients (26). The results of this trial are awaited and will hopefully clarify whether further study of this combination in *EGFR* mutation–negative patients is justified.

Although the plasma drug levels showed considerable interpatient variability, in all patients, erlotinib levels were below the estimated therapeutic level of 1.27 μmol/L and mean plasma levels decreased from day 7 to 21, whereas sorafenib levels remained stable (27). The mechanism for the reduced erlotinib levels remains uncertain. Although several factors may influence erlotinib levels, we did not find a relation with smoking status or concomitant medication. One possible explanation is that the coadministration of sorafenib influenced erlotinib steady-state levels. Two phase I trials similarly reported a significant decreased exposure to the EGFR inhibitors erlotinib and gefinitib by the coadministration of sorafenib, providing support for this explanation (28, 29). No effects of erlotinib and gefitinib on the pharmacokinetic profile of sorafenib were found. The mechanism of this possible drug interaction is unclear. Erlotinib is a substrate for CYP3A4, and our results suggest that CYP3A4 may play a role. Consistent with data showing that CYP3A4*1B is associated with a moderately increased CYP3A4 activity, we found CYP3A4 *1A homozygotes to have higher plasma levels than patients with *1A/*1B and *1B/*1B genotypes (30). Although sorafenib is not a CYP3A4 inducer, one hypothesis is that it may instead cause CYP3A4 activation (28, 31). Unlike induction, activation does not increase the quantity of the CYP3A4 enzyme but increases the velocity of the reaction.

Regardless of the mechanism, our data suggest that the lower erlotinib levels are of clinical importance. This raises the questions of whether higher doses of erlotinib would have further improved outcomes and would have resulted in a higher ORR and longer OS in *EGFR* mutation–negative patients. The inhibition constants of erlotinib and gefitinib are many times higher for wild-type *EGFR* compared with mutated *EGFR* (32–34). The plasma erlotinib levels in *EGFR* mutation–negative patients may therefore have been too low to cause relevant EGFR inhibition. Results from previous trials, such as the phase III BR.21 trial (erlotinib versus placebo), show that some wild-type *EGFR* patients benefit from EGFR inhibitors (35). In addition, a study on human NSCLC lines expressing wild-type *EGFR* found that sensitivity to erlotinib was predicted by a high ratio of phosphorylated *EGFR* expression to phosphorylated AKT (p-EGFR/p-AKT ratio). A high p-EGFR/p-AKT ratio is thought to indicate a high dependency of the NSCLC cells on the activated EGFR axis. These data suggest that there may be patients in whom tumorigenesis is (partially) dependent on wild-type *EGFR* signaling. Coupled with the lower inhibition constant of erlotinib for wild-type *EGFR*, it is thus possible that higher doses of erlotinib would provide further benefit in these wild-type *EGFR* patients. In *EGFR* mutation–positive patients, on the other hand, the "subtherapeutic" erlotinib plasma levels in our study were sufficient to lead to a high response rate. Accordingly, we recently reported a partial response in a patient with an *EGFR*-mutated tumor treated with 50 mg/d erlotinib, achieving a plasma level of 0.89 μmol/L (36). Further evaluation of the mechanism and clinical relevance of this interaction is clearly warranted.

The treatment was generally well tolerated and the adverse events observed are similar to those reported in other trials of these drugs. However, the frequency and severity of diarrhea and hand-foot skin reaction were higher than in published reports (37, 38). The phase I trial of sorafenib and erlotinib in solid tumors reported a cumulative effect of adverse events, with every patient receiving 150 mg/d erlotinib plus 800 mg/d sorafenib ultimately requiring dose reductions, mainly due to fatigue, gastrointestinal problems, and skin toxicity (9). Erlotinib (150 mg/d) plus sorafenib (400 mg/d) was better tolerated for extended periods of time. Unlike for erlotinib, sorafenib-associated diarrhea was found to be a dose-dependent adverse event, and we found sorafenib plasma levels above the median at D21 to be associated with grade 2 to 3 diarrhea (39, 40). Similarly, hand-foot skin reaction increases with cumulative doses of sorafenib (36). The increased diarrhea and hand-foot skin reaction in our study may thus reflect enhanced sorafenib toxicity. The efficacy and safety of lower sorafenib doses in NSCLC are not known. Any future studies of this study combination, therefore, need to further evaluate the efficacy and tolerability with different dosing schedules of sorafenib.

In conclusion, the study primary end point of NPR at 6 weeks >50% was met and shows that sorafenib plus erlotinib has encouraging activity against advanced NSCLC. Although *EGFR* mutation–positive patients benefited most, the results do not seem superior to those achieved with EGFR tyrosine kinase inhibitor monotherapy. In contrast, in *EGFR* mutation–negative patients, the study combination achieved higher response rates than that reported for either agent alone. In addition, erlotinib levels were markedly reduced, possibly due to the coadministration of sorafenib. Further study of this combination as salvage therapy in *EGFR* mutation–negative patients, at least in non-SCC, is warranted. Any future studies need to assess different dose schedules, biomarkers for efficacy, and the mechanism and clinical relevance of the possible drug interaction.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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