DOI:10.1158/1078-0432.CCR-07-0382

Clinical Cancer Research

Phase I Targeted Combination Trial of Sorafenib and Erlotinib in Patients with Advanced Solid Tumors

Ignacio Duran, Sebastien J. Hotté, Holger Hirte, et al.

Clin Cancer Res 2007;13:4849-4857. Published online August 15, 2007.

DOI:10.1158/1078-0432.CCR-07-0382

Phase I Targeted Combination Trial of Sorafenib and Erlotinib in Patients with Advanced Solid Tumors

Ignacio Duran,[1] Sebastien J. Hotté,[1] Holger Hirte,[1] Eric X. Chen,[1] Martha MacLean,[1] Sandra Turner,[1] Lixia Duan,[1] Gregory R. Pond,[1] Chetan Lathia,[3] Scott Walsh,[2] John J. Wright,[4] Janet Dancey,[4] and Lillian L. Siu[1]

Abstract

Purpose: Sorafenib and erlotinib are potent, orally administered receptor tyrosine kinase inhibitors with antiproliferative and antiangiogenic activities. Given their inhibitory target profile and efficacy as single agents, the combination of these drugs is of considerable interest in solid malignancies. This study aimed to determine the recommended phase II dose of this targeted combination, their toxicity profile, pharmacokinetic interaction, and preliminary clinical activities.

Experimental Design: Sorafenib was administered alone for a 1-week run-in period, and then both drugs were given together continuously, with every 28 days considered as a cycle. Three dose levels were assessed.

Results: Seventeen patients with advanced solid tumors received 75 cycles of treatment. The most frequent adverse events of all grades were constitutional and gastrointestinal in nature followed by electrolytes and dermatologic toxicities. Fatigue was the most common adverse event (17 patients; 100%) followed by diarrhea (15 patients; 88%), hypophosphatemia (13 patients; 76%), and acneiform rash (12 patients; 71%). These adverse events were predominantly mild to moderate. The recommended phase II dose of this combination was determined as 400 mg twice daily sorafenib and 150 mg daily erlotinib. Pharmacokinetic analysis revealed no significant effect of erlotinib on the pharmacokinetic profile of sorafenib. Among 15 evaluable patients, 3 (20%) achieved a confirmed partial response and 9 (60%) had stable disease as best response.

Conclusions: Sorafenib and erlotinib are well tolerated and seem to have no pharmacokinetic interactions when administered in combination at their full single-agent recommended doses. This well tolerated combination resulted in promising activity that needs further validation in phase II studies.

Increased understanding of the molecular mechanisms that control tumor cell proliferation, invasion, and metastasis has identified several targets in cancer therapeutics (1). Current efforts in anticancer drug development are focused on the evaluation of agents with activity against several targets and on the concurrent administration of molecule-specific drugs (2).

Authors' Affiliations: [1]Princess Margaret Hospital Phase II Consortium; [2]Division of Dermatology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [3]Bayer Pharmaceuticals Corp., West Haven, Connecticut; and [4]National Cancer Institute, Bethesda, Maryland

Received 2/15/07; revised 4/27/07; accepted 5/22/07.

Grant support: National Cancer Institute Contract Number N01-CM-17107.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note: This study was presented in part in the 18th European Organization for Research and Treatment of Cancer-National Cancer Institute-AACR Symposium on Molecular Targets and Cancer Therapeutics, November 2006, Prague, Czech Republic.

Requests for reprints: Lillian L. Siu, Department of Medical Oncology and Hematology, Princess Margaret Hospital, University Health Network, 610 University Avenue, Suite 5-718, Toronto, Ontario, Canada M5G 2M9. Phone: 416-946-2911; Fax: 416-946-4467; E-mail: lillian.siu@uhn.on.ca.

doi:10.1158/1078-0432.CCR-07-0382

The epidermal growth factor receptor (EGFR) initiates a signal transduction cascade that modulates cellular functions through activation of pathways, such as the mitogen-activated protein kinase and the phosphatidylinositol 3-kinase. The mitogen-activated protein kinase cascade relays extracellular signals from ligand-bound cell surface tyrosine kinase receptors to the nucleus by a series of phosphorylation events beginning with the activation of Ras (3, 4). Activated Ras triggers downstream effectors, including the Raf serine/threonine kinase (5–7). Activated Raf propagates signaling by phosphorylating mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 1/2 and extracellular signal-regulated kinase 1/2, inducing activation of transcription factors involved in regulation of genes critical in proliferation, angiogenesis, and resistance to cytotoxics (8–12). The mitogen-activated protein kinase pathway seems to be dysregulated in several human malignancies, and therefore, many of its critical components represent potential targets for anticancer treatment.

Erlotinib (Tarceva, OSI-774; OSI Pharmaceuticals) is an oral quinazolinamine, which blocks EGFR tyrosine kinase through competitive inhibition at the ATP-binding site (13). A phase I study showed 150 mg daily on a continuous schedule as the recommended dose for phase II studies (RPTD) and reported skin toxicity and diarrhea as dose limiting (14). Erlotinib has shown activity in some tumor types, including head and neck

DOI:10.1158/1078-0432.CCR-07-0382

(15), lung (16), ovarian (17), and endometrial (18) carcinoma. Two randomized phase III trials confirmed survival benefits and have led to drug approval in non–small cell lung cancer and in combination with gemcitabine in pancreatic cancer (19, 20).

Sorafenib (Nexavar, BAY 43-9006; Bayer Pharmaceuticals Corp.) is an oral multitargeted agent with activities against Raf kinase and vascular endothelial growth factor receptor-2 (VEGFR-2), resulting in tumor growth inhibition via interference with cellular proliferation and angiogenesis. Sorafenib also exhibits median inhibitory concentrations (IC_{50}) in nanomolar ranges for other receptor tyrosine kinases, such as VEFGR-3, platelet-derived growth factor receptor-β, Flt-3, and c-KIT (21). Phase I studies of sorafenib determined 400 mg twice daily on a continuous schedule as the RPTD (22–25). Toxicities associated with sorafenib were mild to moderate and included rash, hand-foot syndrome, diarrhea, fatigue, and hypertension. Partial responses were observed in hepatocellular (26) and renal cell cancers (27) with single-agent sorafenib, and disease stabilization has been reported in multiple tumor types, such as melanoma, colorectal, non–small cell lung cancer, and ovarian cancer (22, 24, 25, 28–30). Recently, sorafenib has been approved for the treatment of advanced renal cell cancers.[5] Recent preclinical data showed a dose-dependent synergistic effect in growth inhibition and apoptosis with the concurrent administration of sorafenib and erlotinib, providing a rationale for the clinical development of this combination (31). Yet, definitive molecular data are lacking to explain the mechanisms of synergy, and the relative contributions of the two agents to tumor growth inhibition when administered in combination are uncertain. Given that sorafenib and erlotinib have independently shown anticancer activity in the clinical setting, and the presence of *in vitro* synergism when combined, a phase I trial was conducted to determine the RPTD, safety, and pharmacokinetics of these two targeted agents given together on a continuous schedule.

Materials and Methods

Patient eligibility. Patients were required to have a histologically confirmed malignancy, either metastatic or unresectable. Inclusion criteria included (*a*) age ≥18 years; (*b*) Eastern Cooperative Oncology Group performance status ≤2; (*c*) adequate hematologic, hepatic, and renal function (absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, bilirubin ≤ upper limit of normal, aspartate aminotransferase/alanine aminotransferase ≤2.5 × upper limit of normal, and creatinine ≤ upper limit of normal or creatinine clearance ≥60 mL/min); and (*d*) 4-week interval between study treatment and any prior radiotherapy or chemotherapy. Exclusion criteria included (*a*) prior treatment with sorafenib, erlotinib, or any agents targeting EGFR, Raf, VEGF, or VEGFR; (*b*) major surgery within the last 21 days; (*c*) uncontrolled hypertension (defined as systolic blood pressure >140 mmHg and/or diastolic pressure >90 mmHg in spite of medical treatment) or intercurrent illnesses; (*d*) bleeding diathesis or coagulopathy; (*e*) brain or meningeal metastases; and (*f*) concurrent use of enzyme-inducing antiepileptic drugs or other CYP3A4 inducers.

The institutional review board of both participating centers approved the study, which was conducted in accordance with federal and institutional guidelines.

Study design. This was a dual-agent, open-label, phase I study. Sorafenib was administered alone for a week during a "run-in" period, and then both drugs were given together on a continuous basis with every 28 days considered as a cycle. Three dose levels were planned: (*a*) 200 mg twice daily sorafenib and 100 mg daily erlotinib, (*b*) 200 mg twice daily sorafenib and 150 mg daily erlotinib, and (*c*) 400 mg twice daily sorafenib and 150 mg daily erlotinib. Further dose escalations were not considered because at dose level 3 both drugs would be administered at their RPTD as single agents. No intrapatient dose escalation was permitted.

Three patients were initially enrolled in each dose level, and dose escalation followed the standard 3 + 3 rule. The occurrence of dose-limiting toxicity (DLT) was monitored during the first 28 days while the two agents were given in combination. The RPTD is the dose level in which less than or equal to one of six patients encountered DLT. If the frequency of DLT encountered at the highest dose level did not fulfill the maximum tolerated dose definition, then 400 mg twice daily sorafenib with 150 mg daily erlotinib was to be accepted as the RPTD.

Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 3.0. DLTs were defined as adverse events attributed as being possibly, probably, or definitely related to the study agents, occurring within the first 28 days of their coadministration and fulfilling one of the following criteria: (*a*) any grade 4 hematologic toxicity, (*b*) any nonhematologic toxicity grade ≥3 (except alopecia, nausea, and vomiting responsive to antiemetics or diarrhea responsive to medications), (*c*) any intolerable grade 2 nonhematologic or grade 3 hematologic toxicity requiring a dose reduction during the first 28 days of combination therapy, and (*d*) any toxicity resulting in a treatment delay of >1 week during the first 28 days of combination therapy.

Table 1. Patient characteristics

	Patients (*N* = 17), *n* (%)
Age (y)	
Median	56
Range	30-77
Gender	
Female	8 (47)
Male	9 (53)
ECOG performance status	
0	6 (35)
1	10 (59)
2	1 (6)
Type of tumor	
Neuroendocrine carcinoma	3 (18)
Head and neck squamous cell cancer	2 (6)
Hepatocellular cancer	1 (6)
Small cell lung cancer	1 (6)
Nasopharyngeal cancer	1 (6)
Cholangiocarcinoma	1 (6)
Malignant hemangiopericytoma	1 (6)
Ovarian endometrioid cancer	1 (6)
Unknown primary adenocarcinoma	1 (6)
Thyroid papillary cancer	1 (6)
Bladder transitional cell cancer	1 (6)
Anal canal squamous cell cancer	1 (6)
Skin squamous cell cancer	1 (6)
Duodenum adenocarcinoma	1 (6)
Prior treatment	
Adjuvant chemotherapy	6 (35)
Palliative chemotherapy	10 (59)
Radiotherapy	10 (59)
No. prior chemotherapy regimens	
0	5 (29)
1	3 (18)
2	3 (18)
3	2 (11)
4	3 (18)
>4	1 (6)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

[5] http://www.fda.gov/bbs/topics/NEWS/2005/NEW01282.html

DOI:10.1158/1078-0432.CCR-07-0382

Table 2. Dose delays and reductions due to adverse events per dose level and drug

Patient ID	Dose level	Any delay (yes/no)	Reason of delay	Length of delay (wk)		Any dose reduction (yes/no)		Number/timing of dose reductions
				SOR	ERL	SOR	ERL	
001	1	No	n/a	n/a	n/a	No	No	n/a
002	1	No	n/a	n/a	n/a	No	No	n/a
003	1	No	n/a	n/a	n/a	No	No	n/a
004	2	No	n/a	n/a	n/a	No	No	n/a
005	2	No	n/a	n/a	n/a	No	No	n/a
006	2	No	n/a	n/a	n/a	No	No	n/a
007*	2	No	n/a	n/a	n/a	No	No	n/a
008	2	No	n/a	n/a	n/a	No	No	n/a
009	2	Yes	Fatigue	2	2	Yes	Yes	1 C2D15
010	2	Yes	Diarrhea	1	1	No	Yes	1 C8D28
012*	3	Yes	Fatigue Paronychial inflammation	1	2	Yes	Yes	1 C4D15
013	3	Yes	Diarrhea Skin toxicity Mucositis	6	6	Yes	Yes	2 C2D1;C4D28
014*	3	Yes	Skin toxicity	1	0	Yes	No	1 C2D15
015 †	3	Yes	Grade 2 intolerable diarrhea	2	2	No	No	n/a
016	3	No	N/a	n/a	n/a	No	No	n/a
017	3	Yes	↑Liver enzymes Paronychial inflammation	3+ 2	3+ 2	Yes	Yes	2 C2D5

Abbreviations: SOR, sorafenib; ERL, erlotinib; n/a, not applicable.
*Patients who achieved a partial response.
† This patient had DLT. Study treatment was held due to toxicity with the intention of restarting at a lower dose, but due to disease progression, patient was removed from study and was not rechallenged. Shaded entries represent patients who required dose delays due to toxicity.

Patient evaluation. Pretreatment evaluations were done within 7 days of treatment start and included history and physical examination, performance status, hematology, biochemistry, and urinalysis. Physical examinations were repeated on days 1 and 15 of each cycle, whereas laboratory evaluations were measured weekly for the entire duration of the study.

Baseline radiological investigations were done within 28 days of study start. Response was assessed by Response Evaluation Criteria in Solid Tumors (32) every other cycle and confirmed at least 4 weeks after the initial observation. All responses were independently reviewed.

Dose modifications. Patients were required to meet the following criteria to receive study drugs on day 1 of a treatment cycle: absolute neutrophil count $\geq 1.0 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and nonhematologic toxicity recovered to grade ≤ 1 (or tolerable grade 2). If a DLT occurred in the first cycle, treatment was withheld until toxicity resolved to grade 2 or less. At the investigator's discretion depending on the nature of the adverse event, on toxicity resolution, the dose of one or both drugs could be modified. Patients in whom one study drug was held or discontinued could continue to receive the other. Subjects who failed to recover to grade 0 to 1 or tolerable grade 2 from a treatment-related adverse event within 14 days, or those who required a third dose reduction, discontinued study therapy.

Duration of the therapy. Study treatment continued until disease progression, intercurrent illness that prevented further administration of treatment, unacceptable adverse event, patient's decision to withdraw from the study, or changes in the patient's condition rendering the patient unacceptable for further treatment.

Pharmacokinetic analysis. Blood samples were collected during cycle 1 at day -6 before morning sorafenib dosing; day -2 before dose and at 1, 2, 4, 6, 8, 12, and 24 h after dose; and at the same time points on day 15. Sample analysis for sorafenib was done at Bayer HealthCare Pharmaceuticals using a validated liquid chromatographic mass spectrometric method (23). Lower limit of quantification for sorafenib was 0.1 μg/mL. Plasma pharmacokinetic variables, including area under the plasma concentration-time curve (AUC), maximum concentration (C_{max}), time to maximum concentration (T_{max}), and elimination half-life, were calculated. A noncompartmental method was used to compute pharmacokinetic variables using the KINCALC program developed by Bayer HealthCare. A Wilcoxon signed rank test was used to compare change in pharmacokinetic variables from day -2 to day 15.

Minimum steady-state plasma concentrations (Css,min) for erlotinib and its metabolite OSI-420 were measured on cycle 1 days 15, 16, 22, and 29 using a high-performance liquid chromatography assay (33). Lower limits of quantification were 12.5 ng/mL for erlotinib and 5 ng/mL for OSI-420, respectively.

Results

Patient demographics. Seventeen patients were enrolled on this study and received 75 cycles of treatment (median, 2; range, 1-10). Table 1 shows their baseline demographics.

Dose escalation and maximum tolerated dose. Three, seven, and seven patients were enrolled in dose levels 1, 2, and 3, respectively. No DLT was observed at the first dose level. Three patients were enrolled at dose level 2. Although no DLT was observed, hypophosphatemia grade ≥ 2 was reported in all patients prompting a cohort expansion to gain more experience with this toxicity. One of four additional patients enrolled presented with asymptomatic grade 3 hypophosphatemia, resulting in a DLT. The DLT definition was then amended to exclude asymptomatic grade 3 or 4 correctable electrolyte abnormalities. Replacement with oral phosphate was recommended if serum

DOI:10.1158/1078-0432.CCR-07-0382

Table 3. Adverse events at least possibly related to study treatment

A. Adverse events of all grades at least possibly related to study treatment by dose level

Adverse event	Dose level 1 (all grades)	Dose level 2 (all grades)	Dose level 3 (all grades)
	Cycles, *n* (%)	Cycles, *n* (%)	Cycles, *n* (%)
Total cycles	7	39	29
Constitutional symptoms			
Fatigue	4 (57)	37 (95)	27 (93)
Weight loss	1 (14)	5 (13)	8 (28)
Gastrointestinal			
Mucositis (functional)	0 (0)	15 (38)	5 (17)
Nausea	2 (29)	1 (3)	7 (24)
Vomiting	2 (29)	0 (0)	5 (17)
Dysgeusia	0 (0)	5 (13)	11 (38)
Diarrhea	1 (14)	32 (82)	25 (86)
Constipation	0 (0)	1 (3)	1 (3)
Anorexia	2 (29)	1 (3)	15 (52)
Dyspepsia	0 (0)	11 (28)	1 (3)
Dermatologic			
Rash (desquamation)	0 (0)	9 (23)	4 (14)
Rash (acneiform)	3 (43)	32 (82)	22 (76)
Dry skin	2 (29)	31 (79)	24 (83)
Pruritus	0 (0)	15 (38)	3 (10)
Paronychial inflammation	0 (0)	0 (0)	5 (17)
Subungual splinter hemorrhage	0 (0)	0 (0)	2 (7)
Alopecia (partial)	0 (0)	17 (44)	13 (45)
Hand and foot syndrome	5 (71)	11 (28)	14 (48)
Hair depigmentation	0 (0)	0 (0)	5 (17)
Metabolic			
Hyponatremia	2 (29)	1 (3)	7 (24)
Hypokalemia	0 (0)	5 (13)	2 (7)
Hyperkalemia	0 (0)	2 (5)	2 (7)
Hyperbilirubinemia	0 (0)	1 (3)	12 (41)
ALT	0 (0)	23 (59)	13 (45)
AST	0 (0)	20 (51)	15 (52)
ALP	0 (0)	5 (13)	2 (7)
Hypoalbuminemia	0 (0)	0 (0)	11 (38)
Hypophosphatemia	1 (14)	22 (56)	18 (62)
GGT	0 (0)	0 (0)	6 (21)
Hyperamylasemia	0 (0)	0 (0)	6 (21)
Hematologic			
Anemia	2 (29)	3 (28)	7 (24)
Leukopenia	1 (14)	10 (26)	2 (7)
Thrombocytopenia	0 (0)	6 (15)	2 (7)
Lymphopenia	1 (14)	16 (41)	10 (34)
Neutropenia	0 (0)	6 (15)	1 (3)

(*Continued on the following page*)

phosphate levels were <0.65 mmol/L; this value was selected arbitrarily as no evidence-based guidelines exist in the literature. Six patients were accrued at dose level 3. One was removed from study due to tumor-related hematuria during the run-in period, thus became inevaluable for DLT and necessitating replacement by another patient. From six patients, one developed grade 2 intolerable diarrhea and anorexia on cycle 1 day 24, hence resulting in a DLT. As only one DLT was encountered at dose level 3, 400 mg twice daily sorafenib with 150 mg daily erlotinib given continuously was declared the RPTD. Dose delays and reductions are shown in Table 2.

Safety. The most frequent adverse event of all grades, at least possibly related to study treatment, was constitutional and gastrointestinal in nature followed by electrolytes and dermatologic toxicities (Table 3A and B). Fatigue was the most common observed adverse event occurring in all patients. It was generally mild to moderate and tended to increase at higher dose levels. Diarrhea was the most relevant gastrointestinal toxicity (15 patients; 88%), being grade 1 to 2 in most cases and easily managed with oral loperamide. At dose level 3, however, diarrhea was dose limiting (intolerable grade 2) in one of six patients. Acneiform rash represented the most frequent dermatologic adverse event reported (12 patients; 71%). No direct correlation was observed between higher doses and incidence of this phenomenon. Other cutaneous side effects, previously reported with single-agent administration of sorafenib and erlotinib, were observed. These included xerosis, hair depigmentation, paronychial inflammation, frontal alopecia, splinter subungual hemorrhages, and desquamative rash; most were tolerable and only the paronychial inflammation required intervention. Interestingly, two patients at dose level 3 developed atypical rashes within the first 7 days of combined treatment that were categorized as erythema multiforme-like with edematous plaques and atypical targetoid lesions (Fig. 1A

DOI:10.1158/1078-0432.CCR-07-0382

Table 3. (Cont'd)

A. Adverse events of all grades at least possibly related to study treatment by dose level

Adverse event	Dose level 1 (all grades)	Dose level 2 (all grades)	Dose level 3 (all grades)
	Cycles, *n* (%)	Cycles, *n* (%)	Cycles, *n* (%)
Musculoskeletal			
Joint pain	0 (0)	17 (44)	2 (7)
Myalgia	0 (0)	15 (38)	7 (24)
Arthritis	0 (0)	1 (3)	0 (0)
Others			
Dry eye	0 (0)	18 (46)	7 (24)
Keratitis	0 (0)	10 (26)	0 (0)
Headache	0 (0)	15 (38)	4 (14)
Hypertension	0 (0)	2 (5)	10 (34)
Epistaxis	1 (14)	18 (46)	8 (28)

B. Grade 3-4 adverse events at least possibly related to study treatment by dose level

Adverse event	Dose level 1 (grade 3+)	Dose level 2 (grade 3+)	Dose level 3 (grade 3+)
	Cycles, *n* (%)	Cycles, *n* (%)	Cycles, *n* (%)
Total cycles	7	39	29
Constitutional symptoms			
Fatigue	0 (0)	1 (3)	1 (3)
Gastrointestinal			
Vomiting	0 (0)	0 (0)	1 (3)
Diarrhea	0 (0)	1 (3)	1 (3)
Dermatologic			
Rash (acneiform)	0 (0)	0 (0)	1 (3)
Paronychial inflammation	0 (0)	0 (0)	1 (3)
Metabolic			
Hyponatremia	0 (0)	0 (0)	0 (0)
Hypokalemia	0 (0)	3 (8)	0 (0)
ALT	0 (0)	0 (0)	1 (3)
AST	0 (0)	0 (0)	1 (3)
Hypophosphatemia	0 (0)	6 (15)	10 (34)
PTT	0 (0)	1 (3)	0 (0)
INR increased	0 (0)	0 (0)	1 (3)
Hematologic			
Lymphopenia	0 (0)	4 (10)	0 (0)
Other			
Hematuria	0 (0)	0 (0)	1 (3)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase, PTT, partial thromboplastin time; INR, international normalized ratio.

and B). These rashes resolved after 7 to 10 days and did not require dose modifications. Another notable toxicity was dose-dependent hypophosphatemia, attributed to sorafenib but may also have been exacerbated by the addition of erlotinib. Thirteen patients (76%) across all dose levels presented with different severities of this adverse event, with grade 3 events observed in 6 patients (35%). Joint stiffness was an additional unusual toxicity detected. Two patients at dose level 2 presented with multiple episodes of self-limited stiffness in the temporomandibular and wrist joints, respectively. No grade 3 or 4 vascular events, such as hypertension or bleeding, were observed. There were no toxic deaths on study.

Pharmacokinetic analysis. Fifteen patients were eligible for pharmacokinetic analysis. Mean $AUC_{0\text{-}12}$, T_{max}, C_{max}, and C_{min} values of sorafenib on day -2 and day 15 showed significant intrapatient and interpatient variability. No statistically significant differences in any pharmacokinetic variables of sorafenib were detected in the presence or absence of erlotinib, suggesting a lack of effect of erlotinib on the pharmacokinetic profile of sorafenib (Table 4A; Fig. 2). The average Css,min values of erlotinib and OSI-420 also revealed wide interindividual variability in all dose levels, with mean erlotinib trough levels consistently above 500 ng/mL in the 150 mg group (Table 4B; Fig. 3). Due to the sampling schedule in this study, definitive conclusions about the effect of sorafenib on the pharmacokinetic of erlotinib cannot be drawn.

Efficacy. Tumor response was assessed in 15 patients. Two patients were considered inevaluable; 1 was taken off study due to intercurrent illness not related to treatment after 4 weeks and the other was removed from study due to severe tumor-related hematuria after 4 days. Of the 15 evaluable patients, 3 (20%) achieved a confirmed partial response and 9 (60%) had stable disease as best response. Among the 9 patients with stable disease, the maximum changes in the sum of their target lesions

DOI:10.1158/1078-0432.CCR-07-0382

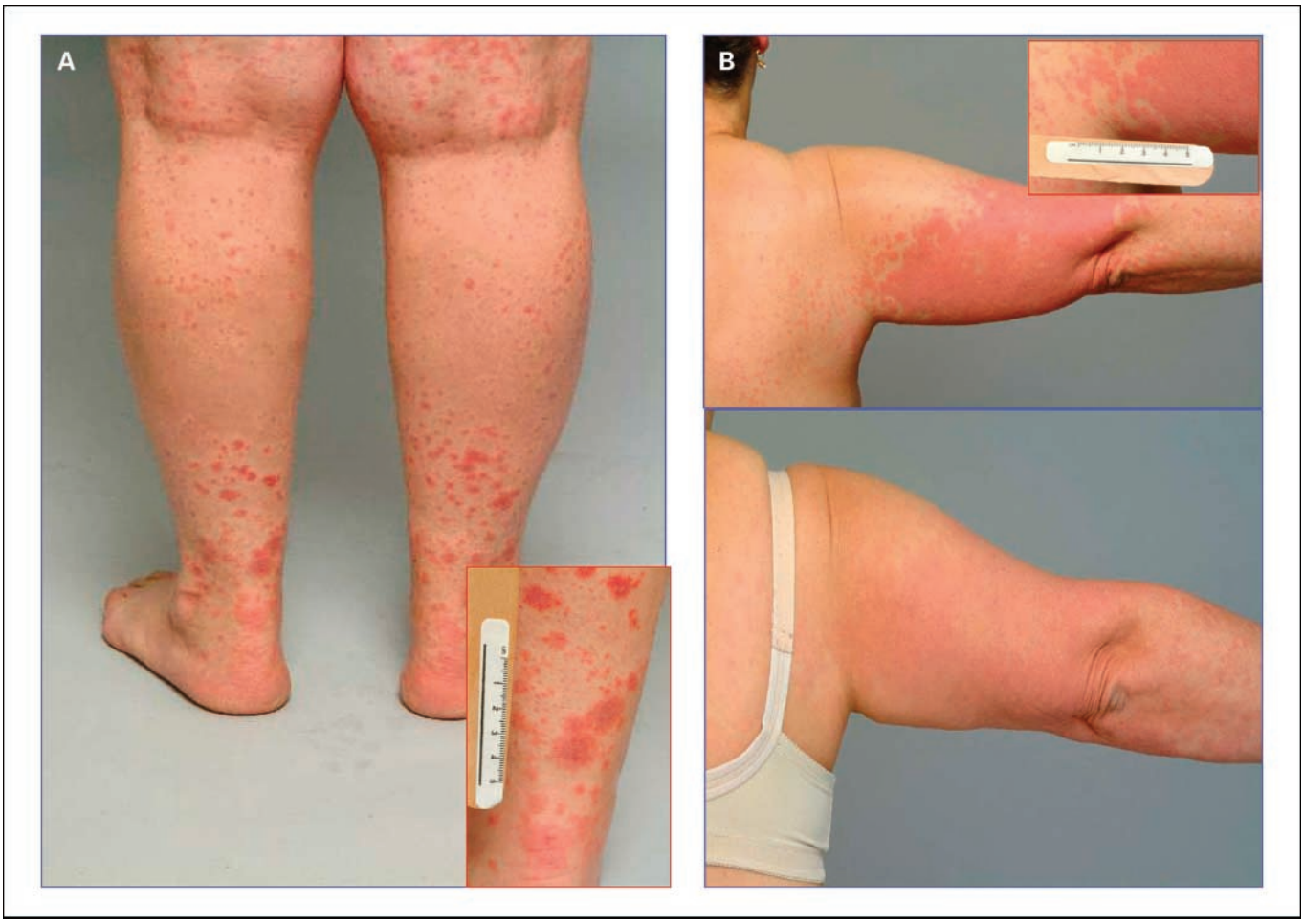

Fig. 1. *A,* patient 014 presenting erythema multiforme-like lesions consisting of urticarial, edematous plaques, and atypical targets after 1 wk on 400 mg twice daily sorafenib and 150 mg daily erlotinib. *B,* resolution of rash in patient 014 after 1 wk with no study drug modification.

ranged from 14.7% shrinkage to 20.0% growth (Fig. 4), and the median duration of stable disease was 3.8 months (range, 2.0 to >8.7 months).

One patient at dose level 2, a 63-year-old female with cholangiocarcinoma and liver metastases, previously treated with gemcitabine and capecitabine for over 15 months, achieved a partial response at cycle 2 that lasted 9.6 months. Two additional patients at dose level 3 experienced a partial response. A 53-year-old female with metastatic small bowel adenocarcinoma had a partial response after two cycles. This patient had a dose reduction in sorafenib due to severe hand-foot syndrome and progressed at the end of cycle 4. The other responder is a 38-year-old male with heavily pretreated pancreatic glucagonoma and liver metastases who achieved a partial response along with significant improvement in his hyperglycemia after cycle 2 and progressed after 10 cycles. Two patients continue on study treatment at the time of this report.

Discussion

The results of this phase I trial showed that sorafenib and erlotinib can be administered safely in combination at their RPTD as single agents, with minimal overlapping toxicity. The most common drug-related adverse event was those expected from each agent independently, including fatigue, rash, dry skin, diarrhea, and hypophosphatemia. These ranged from mild to moderate in severity and were easily manageable. A dose-dependent relationship was observed for certain adverse event, such as fatigue, diarrhea, and hypophosphatemia. Asymptomatic hypophosphatemia was observed at all dose levels and seemed to be more frequent and severe than in single-agent sorafenib studies (27, 34). Whether the addition of erlotinib may have exacerbated the incidence of this adverse event remains unclear. Interestingly, rashes not previously described in the literature with these agents given alone were observed in two patients at the highest dose level.

Although all patients at dose level 3 were able to tolerate full doses of both drugs during their first cycle, a cumulative effect was noticed with every patient requiring dose reductions after one to four cycles, mainly due to fatigue, gastrointestinal, and skin toxicity. In contrast, patients treated at dose level 2 seemed to tolerate this drug combination better for extended durations. Furthermore, anticancer activity was observed in one patient at dose level 2 with a long-lasting partial response. Hence, it is reasonable to begin with the RPTD of this combination at 400 mg twice daily sorafenib and 150 mg daily erlotinib while being wary that those who remain on therapy may require dose modifications of one or both drugs in the longer term. It is

DOI:10.1158/1078-0432.CCR-07-0382

Table 4. Sorafenib and erlotinib pharmacokinetic variables

A. Sorafenib pharmacokinetic variables (mean values and range) by dose level

	Day -2	Day 15	*P*
All dose levels			
n	17	15	
AUC (μg·h/mL)	49.5 (14.4-130.4)	36.8 (18.9-149.8)	0.85
C_{max} (μg/mL)	6.6 (2.1-14.8)	5.1 (2.2-17.2)	0.56
C_{min} (μg/mL)	2.3 (0.7-5.8)	1.6 (0.6-7.7)	0.56
T_{max} (h)	2 (0-12)	2 (0-12)	0.77
Dose levels 1 and 2 (200 mg twice daily sorafenib)			
n	10	10	
AUC (μg·h/mL)	30.3 (14.4-63.4)	30.2 (18.9-100.4)	0.85
C_{max} (μg/mL)	4.0 (2.1-8.0)	4.1 (2.2-9.9)	0.63
C_{min} (μg/mL)	1.6 (0.7-4.3)	1.5 (0.6-6.2)	0.85
T_{max} (h)	2 (0-12)	2 (0-12)	0.84
Dose level 3 (400 mg twice daily sorafenib)			
n	7	5	
AUC (μg·h/mL)	89.2 (50.8-130.4)	86.9 (61.8-149.8)	1.00
C_{max} (μg/mL)	10.9 (6.6-14.8)	11.7 (7.3-17.2)	0.63
C_{min} (μg/mL)	4.6 (3.3-5.8)	4.2 (1.7-7.7)	0.44
T_{max} (h)	4 (0-12)	1 (0-2)	0.31

B. Erlotinib pharmacokinetic variables by dose level

	Mean erlotinib Css, min levels, ng/mL (SD)				Mean OSI-420 Css, min levels, ng/mL (SD)			
	Day 15	Day 16	Day 22	Day 29	Day 15	Day 16	Day 22	Day 29
Dose level 1, *n* = 3 (100 mg daily erlotinib)	287 (293)	301 (483)	367 (428)	486 (403)	53 (27)	52 (65)	42 (48)	53 (35)
Dose levels 2 and 3, *n* = 14 (150 mg daily erlotinib)	389 (426)	567 (626)	800 (629)	755 (827)	48 (51)	75 (78)	92 (82)	83 (90)

debatable whether future phase II studies should compare both dosages for safety and efficacy over a longer period to truly evaluate the effect of cumulative toxicity of this combination.

The pharmacokinetic results of sorafenib and erlotinib obtained were similar to those from single-agent trials, where moderate to significant interpatient variability for both drugs has been described (14, 23, 35, 36). Sorafenib exhibited an early absorption phase followed by delayed secondary peaks that could be attributed to enterohepatic circulation of its glucuronide metabolite and the interconversion of the *N*-oxide metabolite back to the parent compound (Fig. 2). Mean AUC_{0-12}, C_{max}, and C_{min} values for sorafenib were dose dependent but did not vary significantly in the presence or absence of erlotinib, suggesting a lack of effect of erlotinib on sorafenib pharmacokinetics. This is consistent with the lack of major overlapping toxicity in the clinical setting, enabling the delivery of both drugs at their full single-agent doses. The study design and sampling schedule in this study did not permit drawing definitive conclusions of the potential effect of sorafenib on erlotinib pharmacokinetics.

Treatment outcomes in most advanced epithelial neoplasms remain poor in spite of recent progress in molecular biology and development of novel anticancer agents. The diversity of molecular abnormalities is felt to partly contribute to the

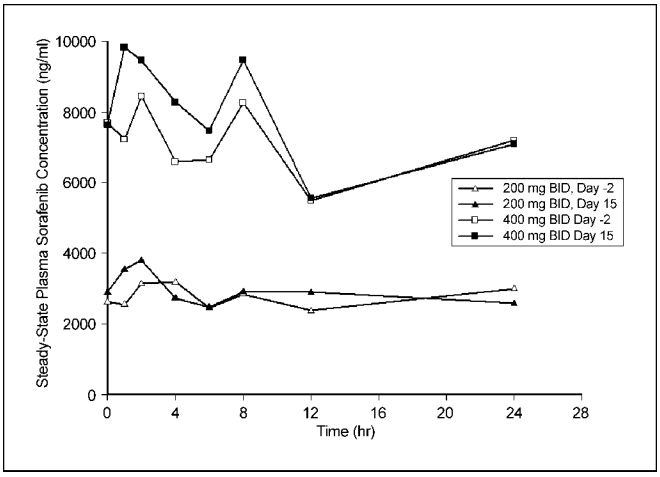

Fig. 2. Mean sorafenib concentrations separated by dose levels and separated by days -2 and 15. Black arrows, plasma dose of sorafenib.

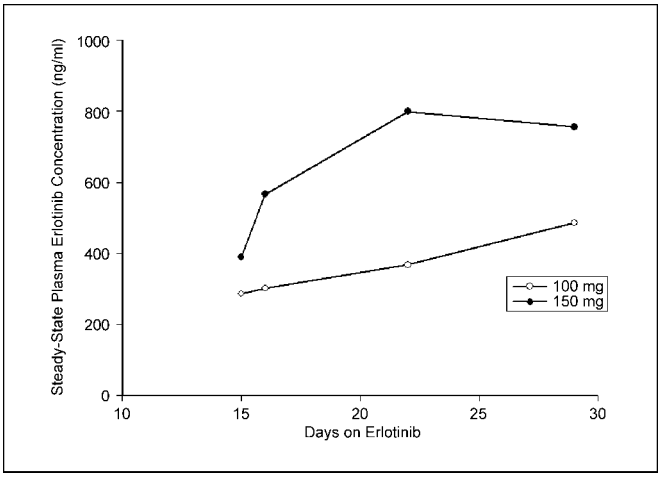

Fig. 3. Mean Css,min erlotinib concentrations separated by dose levels.

DOI:10.1158/1078-0432.CCR-07-0382

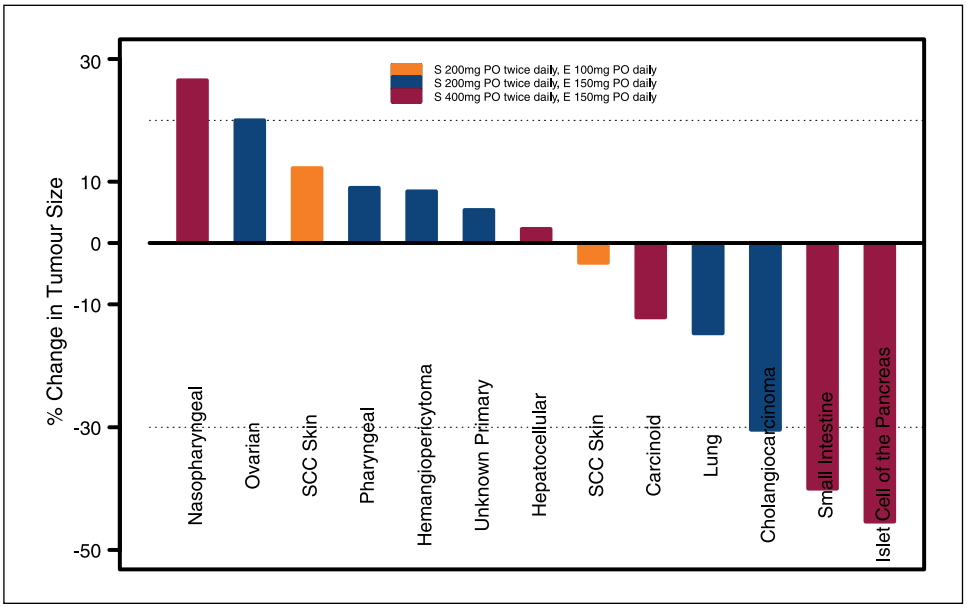

Fig. 4. Waterfall diagram showing changes in tumor size in target lesions in 13 patients. Two patients were excluded from this figure: one had symptomatic progression and one had only nonmeasurable disease.

resistance to therapy; therefore, developing combinations of anticancer drugs that may exhibit synergistic or complementary activity seems a reasonable approach (37). However, many questions still need to be addressed for the successful combination of targeted agents in clinical trials (38, 39). For instance, there is no consensus on the level of preclinical additivity or synergism required with targeted combinations before proceeding with clinical evaluations. Furthermore, there are challenges in the attribution of antitumor activity and/or toxicity to the individual agents versus the combination effect. The enthusiasm around the development of regimens that contain several promising targeted agents must be balanced by the need to do well-designed clinical trials instead of empirical combinations. Factors such as cumulative toxicity and pharmacodynamic and pharmacokinetic end points should be considered to better evaluate combined therapies and their potential effect in clinical practice.

Previous studies have evaluated combinations of sorafenib or erlotinib with other targeted agents. A phase I trial of sorafenib with bevacizumab in patients with advanced renal cell cancer showed a substantial increase in the expected toxicity, particularly with sorafenib-related adverse events. This exacerbation was more pronounced when sorafenib was administered at 400 mg twice daily. Patients at that dose level presented with a constellation of severe hand-foot syndrome, stomatitis, and anorexia, leading to remarkable weight loss and decline in performance status (38, 40). It would appear that dual inhibition of the VEGF-VEGFR axis can lead to an undesirable toxicity profile. When sorafenib was combined with the EGFR tyrosine kinase inhibitor gefitinib in a phase I study of patients with progressive or refractory non–small cell lung cancer (41), modest activity and a tolerable toxicity profile consisting mostly of fatigue, diarrhea, and liver enzyme elevation were reported. Erlotinib has also been previously tested in combination with other targeted drugs, such as bevacizumab, in patients with non–small cell lung cancer and renal cell cancer (42, 43). The toxicity profile was similar in both studies with rash, diarrhea, and proteinuria as the most relevant adverse events, ranging from mild to moderate in severity. These trials of sorafenib plus gefitinib and erlotinib plus bevacizumab seem to echo our findings in their nonoverlapping toxicity profiles, suggesting that simultaneous inhibition of the EGFR and VEGFR axes seems feasible.

The current study combined for the first time sorafenib and erlotinib, and the toxicity profile and preliminary efficacy evaluations revealed encouraging results. Three of 15 evaluable patients achieved confirmed partial response and 9 patients had stable disease as best response. One patient with metastatic cholangiocarcinoma achieved a long-lasting partial response. Recent studies suggested a relevant implication of the EGFR-mitogen-activated protein kinase pathway and the VEGF-VEGFR system in this tumor pathogenesis (44). A phase II trial with erlotinib in advanced cholangiocarcinoma showed modest activity (45) and one with single-agent sorafenib is ongoing.[6] Another confirmed partial response was observed in a patient with heavily pretreated metastatic pancreatic islet cell carcinoma with liver metastases. High expression of EGFR, phosphorylated EGFR, extracellular signal-regulated kinase, and phosphorylated extracellular signal-regulated kinase as well as VEGF-C and its receptors (VEGFR-2/VEGFR-3) has been recently reported in neuroendocrine tumors, suggesting involvement of these molecular mechanisms in tumor growth and metastasis and therefore representing appropriate targets (46, 47). Lastly, a third patient who achieved a confirmed partial response had metastatic small bowel adenocarcinoma. Although no data confirm a relevant role of EGFR, some reports suggest a significant contribution of VEGF and its receptors to tumor growth through angiogenesis promotion in this tumor type (48).

In this phase I trial, patients with 14 different tumor types were enrolled with responses being observed in malignancies outside of the known spectrum where sorafenib and erlotinib have shown single-agent activity. This finding is encouraging and may launch evaluation opportunities in these and other tumor sites.

[6] http://www.clinicaltrials.gov/ct/show/NCT00238212

DOI:10.1158/1078-0432.CCR-07-0382

References

1. Broxterman HJ, Georgopapadakou NH. Anticancer therapeutics: "addictive" targets, multi-targeted drugs, new drug combinations. Drug Resist Updat 2005;8:183–97.
2. Arteaga CL. Molecular therapeutics: is one promiscuous drug against multiple targets better than combinations of molecule-specific drugs? Clin Cancer Res 2003;9:1231–2.
3. Beeram M, Patnaik A, Rowinsky EK. Raf: a strategic target for therapeutic development against cancer. J Clin Oncol 2005;23:6771–90.
4. Sridhar SS, Hedley D, Siu LL. Raf kinase as a target for anticancer therapeutics. Mol Cancer Ther 2005;4:677–85.
5. Campbell SL, Khosravi-Far R, Rossman KL, et al. Increasing complexity of Ras signaling. Oncogene 1998;17:1395–413.
6. Marshall CJ. Ras effectors. Curr Opin Cell Biol 1996;8:197–204.
7. Khosravi-Far R, Campbell S, Rossman KL, Der CJ. Increasing complexity of Ras signal transduction: involvement of Rho family proteins. Adv Cancer Res 1998;72:57–107.
8. Chong H, Vikis HG, Guan KL. Mechanisms of regulating the Raf kinase family. Cell Signal 2003;15:463–9.
9. Lewis TS, Shapiro PS, Ahn NG. Signal transduction through MAP kinase cascades. Adv Cancer Res 1998;74:49–139.
10. Ahn NG, Seger R, Bratlien RL, et al. Multiple components in an epidermal growth factor-stimulated protein kinase cascade. *In vitro* activation of a myelin basic protein/microtubule-associated protein 2 kinase. J Biol Chem 1991;266:4220–7.
11. Crews CM, Alessandrini A, Erikson RL. The primary structure of MEK, a protein kinase that phosphorylates the ERK gene product. Science 1992;258:478–80.
12. Kerkhoff E, Rapp UR. Cell cycle targets of Ras/Raf signalling. Oncogene 1998;17:1457–62.
13. Sausville EA, Elsayed Y, Monga M, Kim G. Signal transduction-directed cancer treatments. Annu Rev Pharmacol Toxicol 2003;43:199–231.
14. Hidalgo M, Siu LL, Nemunaitis J, et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. J Clin Oncol 2001;19:3267–79.
15. Soulieres D, Senzer NN, Vokes EE, et al. 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.
16. Miller VA, Patel J, Shah N, et al. The epidermal growth factor receptor tyrosine kinase inhibitor erlotinib (OSI-774) shows promising activity in patient with brochioloalveolar cell carcinoma (BAC): preliminary results of a phase II trial. Proc Am Soc Clin Oncol 2003;22:a2491.
17. Finkler N, Gordon A, Crozier M, et al. Phase 2 evaluation of OSI-774, a potent oral antagonist of the EGFR-TK in patients with advanced ovarian carcinoma. Proc Am Soc Clin Oncol 2001;20:A831.
18. Jasas K, Fyles A, Elit L, et al. Phase II study of erlotinib (OSI 774) in women with recurrent or metastatic endometrial cancer: NCIC CTG IND-148. Proc Am Soc Clin Oncol 2004;23:452.
19. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123–32.
20. Moore MJ. Brief communication: a new combination in the treatment of advanced pancreatic cancer. Semin Oncol 2005;32:5–6.
21. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004;64:7099–109.
22. Strumberg D, Richly H, Hilger RA, et al. Phase I clinical and pharmacokinetic study of the novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. J Clin Oncol 2005;23:965–72.
23. Moore M, Hirte HW, Siu L, et al. Phase I study to determine the safety and pharmacokinetics of the novel Raf kinase and VEGFR inhibitor BAY 43-9006, administered for 28 days on/7 days off in patients with advanced, refractory solid tumors. Ann Oncol 2005;16:1688–94.
24. Awada A, Hendlisz A, Gil T, et al. Phase I safety and pharmacokinetics of BAY 43-9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumours. Br J Cancer 2005;92:1855–61.
25. Clark JW, Eder JP, Ryan D, et al. Safety and pharmacokinetics of the dual action raf kinase and vascular endothelial growth factor receptor inhibitor, BAY 43-9006, in patients with advanced, refractory solid tumors. Clin Cancer Res 2005;11:5472–80.
26. Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006;24:4293–4300.
27. Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2006;24:2505–12.
28. Eisen T, Ahmad T, Flaherty KT, et al. Sorafenib in advanced melanoma: a phase II randomised discontinuation trial analysis. Br J Cancer 2006;95:581–6.
29. Strumberg D, Voliotis D, Moeller JG, et al. Results of phase I pharmacokinetic and pharmacodynamic studies of the Raf kinase inhibitor BAY 43-9006 in patients with solid tumors. Int J Clin Pharmacol Ther 2002;40:580–1.
30. Siu LL, Awada A, Takimoto CH, et al. Phase I trial of sorafenib and gemcitabine in advanced solid tumors with an expanded cohort in advanced pancreatic cancer. Clin Cancer Res 2006;12:144–51.
31. Martinelli E, Troiani T, Laus G, et al. Synergistic antitumor activity of the combination of the multitargeted tyrosine kinase inhibitor sorafenib and of EGFR inhibitors in human colon and lung cancer cell lines. Eur J Cancer 2006;4:123.
32. 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.
33. Zhang W, Siu LL, Moore MJ, Chen EX. Simultaneous determination of OSI-774 and its major metabolite OSI-420 in human plasma by using HPLC with UV detection. J Chromatogr B Analyt Technol Biomed Life Sci 2005;814:143–7.
34. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125–34.
35. Lu JF, Eppler SM, Wolf J, et al. Clinical pharmacokinetics of erlotinib in patients with solid tumors and exposure-safety relationship in patients with non-small cell lung cancer. Clin Pharmacol Ther 2006;80:136–45.
36. Miller AA, Murry DJ, Hollis DR, et al. Phase I study of erlotinib (E) for solid tumors in patients with hepatic or renal dysfunction (HD or RD): CALGB 60101. Proc Am Soc Clin Oncol 2006;24:127s.
37. Adjei AA. Novel combinations based on epidermal growth factor receptor inhibition. Clin Cancer Res 2006;12:4446–50s.
38. Sosman JA, Puzanov I, Atkins MB. Opportunities and obstacles to combination targeted therapy in renal cell cancer. Clin Cancer Res 2007;13:764–9s.
39. Dancey JE, Chen HX. Strategies for optimizing combinations of molecularly targeted anticancer agents. Nat Rev Drug Discov 2006;5:649–59.
40. Sosman JA, Flaherty K, Atkins MB, et al. A phase I/II trial of sorafenib (S) with bevacizumab (B) in metastatic renal cell cancer (mRCC) patients (Pts). Proc Am Soc Clin Oncol 2006;24:128s.
41. Adjei AA, Mandrekar S, Marks RS, et al. A phase I study of BAY 43-9006 and gefitinib in patients with refractory or recurrent non-small-cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 2005;23:208s.
42. Herbst RS, Johnson DH, Mininberg E, et al. Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer. J Clin Oncol 2005;23:2544–55.
43. Hainsworth JD, Sosman JA, Spigel DR, et al. Treatment of metastatic renal cell carcinoma with a combination of bevacizumab and erlotinib. J Clin Oncol 2005;23:7889–96.
44. Sirica AE. Cholangiocarcinoma: molecular targeting strategies for chemoprevention and therapy. Hepatology 2005;41:5–15.
45. Philip PA, Mahoney MR, Allmer C, et al. Phase II study of erlotinib in patients with advanced biliary cancer. J Clin Oncol 2006;24:3069–74.
46. Shah T, Hochhauser D, Frow R, et al. Epidermal growth factor receptor expression and activation in neuroendocrine tumours. J Neuroendocrinol 2006;18:355–60.
47. Hansel DE, Rahman A, Hermans J, et al. Liver metastases arising from well-differentiated pancreatic endocrine neoplasms demonstrate increased VEGF-C expression. Mod Pathol 2003;16:652–9.
48. Brown LF, Berse B, Jackman RW, et al. Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in adenocarcinomas of the gastrointestinal tract. Cancer Res 1993;53:4727–35.