Cancer Chemother Pharmacol (2012) 69:333–339
DOI 10.1007/s00280-011-1685-x

ORIGINAL ARTICLE

Phase IB study of sorafenib in combination with gemcitabine and cisplatin in patients with refractory solid tumors

B. Schultheis · G. Kummer · M. Zeth · E. Brendel · C. Xia · M. Kornacker · D. Strumberg

Received: 26 February 2011 / Accepted: 24 May 2011 / Published online: 8 July 2011

Abstract
Purpose Sorafenib (BAY 43-9006), a multikinase inhibitor, has been shown to inhibit tumor growth and tumor angiogenesis by targeting Raf kinase, vascular endothelial growth factor receptor, and platelet-derived growth factor receptor. This study investigated the safety, pharmacokinetics, and preliminary efficacy of sorafenib in combination with gemcitabine and cisplatin.
Methods Patients with advanced solid tumors were treated with 75 mg/m^2 cisplatin on day 1 and 1,250 mg/m^2 gemcitabine on days 1 and 8 of each 21-day cycle. On day 5 of cycle 1, sorafenib 400 mg twice daily was started and continued throughout the complete treatment cycles without interruption.
Results Nineteen patients were valid for safety analysis. The most frequent toxicities related to the cytotoxic agents were hematological disorders. Sorafenib-related toxicities were skin-related, gastrointestinal, and constitutional symptoms. No clinically relevant pharmacokinetic drug–drug interaction between sorafenib, cisplatin, and gemcitabine was detected. $AUC_{0\text{-}72}$ and C_{max} of total and unbound platinum were only marginally changed by concomitant sorafenib. Concomitant sorafenib increased mean AUC and C_{max} of gemcitabine by 12 and 21%.
Conclusions Sorafenib as continuous oral treatment in combination with gemcitabine and cisplatin demonstrated an acceptable safety profile. No clinically relevant pharmacokinetic interaction was detected. Preliminary antitumor activity, pharmacokinetic, and safety data support the recommendation of 400 mg sorafenib twice daily in combination with cisplatin and gemcitabine to be further evaluated in clinical studies.

Keywords Phase I · Sorafenib · Gemcitabine · Cisplatin · Multiple kinase inhibitor · Pharmacokinetics

B. Schultheis (✉) · G. Kummer · M. Zeth · D. Strumberg
Department of Haematology and Medical Oncology,
University of Bochum (Marienhospital Herne),
Hoelkeskampring 40, 44625 Herne, Germany
e-mail: beate.schultheis@marienhospital-herne.de

E. Brendel
Bayer HealthCare Pharmaceuticals, Wuppertal, Germany

C. Xia
Bayer HealthCare Pharmaceuticals, Montville, NJ, USA

M. Kornacker
Bayer HealthCare Pharmaceuticals, Berlin, Germany

Introduction

Sorafenib (BAY 43-9006; Nexavar) is an oral multikinase inhibitor targeting the serine/threonine kinase Raf (Raf-1, wild-type B-Raf and *b-raf* V600E) and the vascular endothelial growth factor receptor (VEGFR)-1/-2/-3, platelet-derived growth factor receptor-β (PDGFR-β) and Flt-3, c-Kit, and p38 tyrosine kinases [1]. For systemic first-line therapy in patients with advanced non-small-cell lung cancer (NSCLC), a platinum-based two-drug combination of cytotoxic drugs still represents the standard of care [2, 3]. Cisplatin and gemcitabine were demonstrated to be superior to cisplatin plus etoposide [4] as well as mitomycin, ifosfamide plus cisplatin chemotherapy [5] in the treatment of advanced NSCLC. The value of cisplatin and gemcitabine combination therapy has been proven for other solid tumors as well [6]. Adding sorafenib, an oral multikinase inhibitor targeting both tumor cells and the tumor vasculature, to the chemotherapy regimen may improve the survival of patients with advanced NSCLC [7]. The combination of

sorafenib with platinum-based cytotoxic drugs such as oxaliplatin and carboplatin was investigated in earlier phase I studies and proved to be safe and well tolerated [8, 9]. The resulting recommended dose of sorafenib in combination with platinum-based cytotoxic drugs was equal to its approved dose as a single-agent therapy, i.e., 400 mg two times a day (BID).

This phase IB clinical study had the objective to investigate the safety profile of sorafenib as continuous oral treatment in combination with gemcitabine and cisplatin in patients with stage IIIB or stage IV NSCLC or other advanced solid tumors and to determine the impact of the combined administration on the pharmacokinetics of sorafenib, gemcitabine, and cisplatin.

Patients and methods

Main eligibility criteria

Eligible patients were ≥18 years of age, with a life expectancy of at least 12 weeks, and a with stage IIIB or stage IV NSCLC or other advanced, histologically or cytologically confirmed solid tumor that was refractory to standard treatment or without standard therapeutic options (like, e.g., patients with a high tumor load and potentially curative option). Patients had to have Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients might have had any number of prior systemic therapy, radiotherapy, or surgery, but patients had to have fully recovered from toxic effects of previous therapies with the exception of alopecia.

Other eligibility criteria included the following: (1) adequate hematopoietic function [absolute neutrophil count (ANC) ≥1,500 μl^{-1}, platelet count ≥100,000 μl^{-1}, and hemoglobin ≥9.0 g dl^{-1}], hepatic function [total bilirubin ≤1.5 times the upper limit of normal (ULN), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) ≤2.5 times ULN; prothrombin time and international normalized ratio of partial thromboplastin time <1.5 times ULN unless on therapeutic anticoagulants)], and renal function (creatinine clearance ≥60 ml min^{-1}); (2) no pregnancy or breast feeding; (3) no clinically relevant comorbidity such as cardiovascular diseases, sensory neuropathy interfering with function, hearing impairment, dehydration, thrombotic, or embolic events and no clinically relevant comedication; (4) no National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 3) [10] grade >2 pulmonary hemorrhage/bleeding, CTCAE grade >3 other hemorrhage/bleeding, or CTCAE grade >2 serious infection within 4 weeks of the first dose of study drug; (5) no progressive or symptomatic brain metastases, patients with neurological symptoms had to have prior imaging to exclude any new or progressive brain metastases.

The study was conducted in accordance with ICH-GCP. All patients provided written informed consent in accordance with federal and institutional guidelines before study treatment.

Study design and treatment

This was a single center, open-label, non-controlled, phase IB study to investigate the safety profile and potential pharmacokinetic interaction of sorafenib as continuous oral treatment in combination with gemcitabine and cisplatin in patients with stage IIIB or stage IV NSCLC or other advanced solid tumors and to determine the impact of the combined administration on the pharmacokinetics of sorafenib, gemcitabine, and cisplatin. A treatment cycle was defined as 21 days. All patients received 75 mg/m^2 cisplatin on day 1 and concurrently 1,250 mg/m^2 gemcitabine on days 1 and 8 of cycle 1. On days 5 through 21 of cycle 1, patients received 400 mg sorafenib orally BID. In cycles 2 through 6, patients received 400 mg sorafenib BID on days 1 through 21, 75 mg/m^2 cisplatin on day 1 and 1,250 mg/m^2 gemcitabine on days 1 and 8. From cycle 7 onwards, the combination treatment was discontinued and sorafenib as single agent could be continued at the discretion of the investigator. Patients had to meet the following criteria to receive subsequent cycles of combination treatment: ANC ≥1.5×10^9 l^{-1}; platelet count ≥100×10^9 l^{-1}; AST, ALT, and bilirubin of CTCAE grade ≤2; other non-hematological toxicities (except alopecia) recovered to CTCAE grade ≤2 or to baseline grade; neurological toxicities recovered to CTCAE grade ≤2. Doses of sorafenib, gemcitabine, and cisplatin could be decreased based on the worst grade of toxicity. Adverse events were assessed at the end of each cycle and graded according to CTCAE, version 3 [10].

Patient evaluation

History, physical examinations, hematological, and biochemical laboratory evaluations were performed at screening, on days 1, 8, and 21 of cycle 1 and day 8 of subsequent cycles. Baseline objective tumor measurements were performed within 4 weeks prior to study treatment. Indicator lesions were selected and monitored throughout the study by the same assessor and using the same technique. Tumor response was evaluated according to RECIST [11].

Pharmacokinetics

Patients with at least one valid pharmacokinetic profile were valid for pharmacokinetic analyses. Plasma samples

were collected at predose and 0.5, 1, 2, 4, 8, 10, and 12 h postdose on day 21 of cycle 1 and day 1 of cycle 2 for sorafenib; at predose and 0.5, 1 (end of infusion), 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 h postdose on day 1 through 4 of cycle 1 and cycle 2 for total and unbound platinum; and at predose and 0.25, 0.5 (end of infusion), 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 96 h postdose on day 1 through 5 of cycle 1 and cycle 2 for gemcitabine and its inactive metabolite 2′-deoxy-2′,2′-difluorouridine (dFdU).

Plasma samples were analyzed for sorafenib using a validated LC–MS–MS analytical method with a lower limit of quantitation (LLOQ) of 0.01 mg l^{-1}. Mean accuracy ranged from 97.2 to 104% and mean precision from 2.8 to 6.6%. Plasma concentrations of gemcitabine and dFdU were also determined using a validated LC/MS/MS assay method with a LLOQ of 0.005 mg l^{-1} for both compounds. Mean accuracy ranged from 95.6 to 99.2% (gemcitabine) and 94.5 to 107% (dFdU), and a mean precision from 2.9 to 7.5% (gemcitabine) and 9.3 to 12.3% (dFdU), respectively.

Total and unbound platinum were quantified using a flameless atomic absorption spectrometric assay, total platinum in plasma with a LLOQ of 0.05 mg l^{-1}, and unbound platinum in ultrafiltrate with a LLOQ of 0.005 mg l^{-1}. Mean accuracy ranged from 90.5 to 113% for total platinum with a mean precision of ≤8.9%. For unbound platinum, mean accuracy ranged from 93.0 to 102% with a mean precision of ≤15.8%.

The following pharmacokinetic parameters were calculated by non-compartmental methods using WinNonlin version 4.1.a (Pharsight Corporation).

Sorafenib

Area under the curve from time 0 to 12 h after dosing ($AUC_{0–12}$) and maximum plasma concentration (C_{max}).

Total and unbound platinum

Area under the curve from time 0 to 72 h after dosing ($AUC_{0–72}$) and C_{max}.

Gemcitabine and dFdU

Area under the curve from time 0 to infinity (AUC) for gemcitabine, area under the curve from time 0 to 96 h after dosing ($AUC_{0–96}$) for dFdU as well as $C_{max.}$ AUC, and partial AUC were calculated applying the linear-logarithmic trapezoidal rule. Pharmacokinetic parameters were analyzed using descriptive statistics.

Table 1 Patient characteristics at baseline

	All subjects valid for safety analysis (n = 19)
Age (years)	
Median	64
Range	44–76
Gender	
Male, *n* (%)	16 (84)
Female, *n* (%)	3 (16)
ECOG performance status	
Grade 0, *n* (%)	9 (47)
Grade 1, *n* (%)	9 (47)
Grade 2, *n* (%)	1 (5)
Type of cancer	
Non-small-cell lung cancer, *n* (%)	12 (63)
Pancreatic cancer, *n* (%)	5 (26)
Hypopharynx/larynx cancer, *n* (%)	1 (5)
Cancer of unknown origin, *n* (%)	1 (5)
Prior anticancer therapy	
Systemic, *n* (%)	7 (37)
Radiotherapy, *n* (%)	2 (11)
Surgery, *n* (%)	18 (95)

Results

Patient characteristics

A total of 19 patients (3 women, 16 men) with advanced solid tumors (12 with NSCLC, 5 with pancreatic cancer) received at least one dose of study drug and were eligible for safety analysis, 12 were eligible for efficacy analysis (having completed two treatment cycles), and 13 for pharmacokinetic analysis. Table 1 summarizes the demographic characteristics of all 19 patients. Those 7 patients having been exposed to previous chemotherapy had received a median of one treatment schedule (range 1–3). The median extent of exposure to sorafenib, gemcitabine, and cisplatin per cycle, i.e., the actual daily dose, was identical or close to the planned exposure, with dose reductions detailed in Table 3. The median number of cycles of study drug treatment was 3, and the median duration of sorafenib treatment was 50 days.

Safety

Table 2 summarizes treatment-emergent adverse events assessed as related to at least one of the three study drugs.

Table 2 Incidence of patients with study drug-related adverse events by worst CTCAE grade

NCI CTCAE category	CTCAE grades 1–2	CTCAE grades 3–4	All CTCAE grades
NCI CTCAE term	*n* (%)	*n* (%)	*n* (%)
Neutrophils	8 (42)	6 (32)	14 (74)
Hemoglobin	1 (5)	2 (11)	3 (16)
Platelets	3 (16)	14 (74)	17 (89)
Leukocytes	4 (21)	6 (32)	10 (53)
Constitutional symptoms	2 (11)	1 (5)	3 (15)
Weight loss	1 (5)		1 (5)
Constitutional symptoms—other	2 (11)	1 (5)	3 (15)
Infection		1 (5)	3 (15)
Infection (clinical), blood	1 (5)		2 (10)[a]
Febrile neutropenia[a]		1 (5)[a]	2 (10)[a]
Gastrointestinal	1 (5)	3 (16)	4 (21)
Anorexia		1 (5)	1 (5)
Diarrhea	1 (5)	1 (5)	2 (10)
Vomiting		1 (5)	1 (5)
Metabolic/laboratory		1 (5)	1 (5)
Creatinine		1 (5)	1 (5)
Pulmonary/upper respiratory		1 (5)	1 (5)
Pulmonary—other		1 (5)	1 (5)
Dermatology/skin	2 (11)	3 (16)	5 (26)
Hand–foot–skin reaction	1 (5)		1 (5)
Exfoliative dermatitis		1 (5)	1 (5)
Rash	1 (5)	3 (16)	4 (21)

[a] There was one CTCAE grade 5 study drug-related adverse event reported in this study: a 76-year-old woman with stage IV NSCLC experienced study drug-related febrile neutropenia and sepsis resulting in death during cycle 2

Although 15 out of 19 patients experienced an adverse event CTC grade 3 or 4, all of those were clinically mild to moderate and mostly manageable in an outpatient setting, with hematotoxicity being the most frequent event. There was only one CTCAE grade 5 study drug-related adverse event reported in this study; a 76-year-old woman with stage IV non-small-cell lung cancer experienced study drug-related febrile neutropenia and sepsis resulting in death during cycle 2.

However, 11 out of 19 patients discontinued study treatment at a certain time point with at least one of the three study drugs due to adverse events. In two of these patients, those adverse events were considered related to sorafenib. These sorafenib-related adverse events were, as expected, generally skin-related. Rash occurred in 4 patients (21%, 3 patients (16%) grade 3 & 4), whereas hand–foot–skin reaction was shown in a single patient of grade 2 CTC. In addition, exfoliative dermatitis grade 3 was also observed in one patient. All other sorafenib-related toxicities were reported in single patients only. All these sorafenib-related AEs were clinically manageable and resolved upon interruption of dosing. Permanent sorafenib dose reduction was necessary in one patient.

Table 3 Dose intensity given per treatment cycle

	Cisplatin	Gemcitabine	Sorafenib
	Median % (range)	Median % (range)	Median % (range)
Cycle 1 ($n = 19$)	100 (75–100)	100 (50–100)	100 (21–100)
Cycle 2 ($n = 13$)	100 (75–100)	100 (50–100)	100 (67–100)
Cycle 3 ($n = 9$)	75 (75–100)	100 (75–100)	100 (50–100)
Cycle 4 ($n = 7$)	75 (75–100)	100 (50–100)	100 (50–100)

Bone marrow-related AEs CTC grade 3–4 occurred in 14 (74%) patients, most frequently related to thrombocytopenia (14 out of 19 patients). Only one out of these patients experienced a bleeding CTC grade 2. Another patient had GI bleeding that was not related to thrombocytopenia. Leukopenia CTC grade 3–4 was associated with fever in 2 out of 6 patients and resulted in death of one patient with NSCLC.

Other abnormal laboratory values and constitutional or gastrointestinal symptoms observed during the course of the study were clearly explained by the subject's medical condition prior to study entry.

Taken together, although the majority of patients experienced study drug-related adverse events, these events were generally clinically mild or moderate and mostly manageable in an outpatient setting.

As the combination of cisplatin, gemcitabine, and sorafenib is not untoxic, we further analyzed the dose intensity applied in individual treatment cycles. As shown in Table 3, the majority of patients who tolerated the initial treatment, even with dose reductions, could proceed with it. Those patients were stopped either because of progressive disease or their personal wish.

Pharmacokinetics

The pharmacokinetic properties of sorafenib following multiple dosing of 400 mg sorafenib twice daily were not or not significantly influenced by concomitant intravenous infusions of 75 mg/m² cisplatin and of 1,250 mg/m² gemcitabine when compared with the administration of sorafenib alone (Table 4). The mean AUC_{0-72} and C_{max} values of total and unbound platinum administered in combination with sorafenib and gemcitabine were only marginally changed compared to the administration without concomitant sorafenib (Table 5).

Table 4 Pharmacokinetic parameters of sorafenib in plasma following oral doses of 400 mg sorafenib BID given either alone or in combination with 75 mg/m^2 cisplatin and 1250 mg/m^2 gemcitabine [geometric mean/%CV (range)]

Parameter	Unit	*n*	Sorafenib alone	Sorafenib combined with gemcitabine and cisplatin	Ratios of combined treatment versus sorafenib alone	90% confidence intervals
AUC_{0-12}	(mg h l^{-1})	13	75.6/30 (43.2–117)	76.6/36 (38.5–136)	1.01	0.86–1.20
C_{max}	(mg l^{-1})	13	9.97/28 (5.70–14.9)	8.95/34 (5.50–15.7)	0.90	0.75–1.07

Table 5 Pharmacokinetic parameters of total and unbound platinum following an intravenous dose of 75 mg/m^2 cisplatin administered together with an intravenous dose of 1,250 mg/m^2 gemcitabine before and after multiple oral doses of 400 mg sorafenib BID [geometric mean/%CV (range)]

Parameter	Unit	*n*	Cisplatin with gemcitabine without sorafenib	Cisplatin with gemcitabine together with sorafenib	Ratios of combined treatment versus cisplatin plus gemcitabine alone	90% confidence intervals
Total platinum						
AUC_{0-72}	(mg h l^{-1})	13	91.1/17 (75.1–142)	95.1/33 (46.1–165)	1.04	0.93–1.18
C_{max}	(mg l^{-1})	13	3.54/22 (2.56–5.07)	3.62/33 (2.19–6.28)	1.02	0.88–1.19
Unbound platinum						
AUC_{0-72}	(mg h l^{-1})	12	3.93/33 (1.63–5.83)	3.89/47 (1.70–8.28)	0.94[a]	0.77–1.14[a]
C_{max}	(mg l^{-1})	13	2.08/28 (1.01–3.42)	2.25/30 (1.31–3.70)	1.08	0.92–1.28

[a] $n = 11$

Table 6 Pharmacokinetic parameters of gemcitabine and 2′-deoxy-2′,2′-difluorouridine (dFdU) following an intravenous dose of 1250 mg/m^2 gemcitabine administered together with an intravenous dose of 75 mg/m^2 cisplatin before and after multiple oral doses of 400 mg sorafenib BID [geometric mean/%CV (range)]

Parameter	Unit	*n*	Gemcitabine with cisplatin without sorafenib	Gemcitabine with cisplatin together with sorafenib	Ratios of combined treatment versus gemcitabine plus cisplatin alone	90% confidence intervals
Gemcitabine						
AUC	(mg h l^{-1})	13	13.3/44 (7.18–29.4)	15.0/43 (7.33–35.9)	1.12	0.89–1.41
C_{max}	(mg l^{-1})	13	20.7/57 (6.27–51.0)	25.1/51 (10.3–56.1)	1.21	0.84–1.73
dFdU						
AUC_{0-96}	(mg h l^{-1})	13	353/41 (130–609)	285/55 (132–677)	0.81	0.66–0.99
C_{max}	(mg l^{-1})	13	38.2/16 (30.3–47.4)	32.7/25 (17.4–43.9)	0.86	0.75–0.98

Mean AUC and C_{max} of gemcitabine were slightly increased by 12 and 21%, respectively, upon concomitant treatment with sorafenib. However, the corresponding 90% confidence intervals included 1.0 (Table 6). Thus, these small increases could not be distinguished from random variability. For dFdU, the inactive metabolite of gemcitabine, modest decreases in AUC_{0-96} and C_{max} were observed upon coadministration of sorafenib with 19% for AUC_{0-96} and 14% for C_{max} on average. The 90% confidence intervals for these two parameters did not include 1.0 (Table 6). Therefore, the differences cannot be regarded as random variability. However, it appears doubtful that these modest changes in AUC_{0-96} and C_{max} would be of clinical relevance.

In conclusion, no clinically relevant pharmacokinetic drug–drug interaction between sorafenib, cisplatin, and gemcitabine was detected.

Efficacy

A total of 12 patients were evaluable for antitumor efficacy, evaluated after two completed treatment cycles. Those 7 patients, non-eligible, had to stop treatment in cycles 1 or 2 due to side effects or unrelated comorbidities (3 patients

each) and to progressive disease (1 patient). Six of the 12 evaluable patients had a NSCLC and had not received previous chemotherapy. Two out of these 6 patients showed a partial response (PR), and 3 additional patients had stabilization of progressive disease (SD) on study entry. The median progression-free survival (PFS) of these 6 patients with NSCLC was 109.5 days.

Four patients presented with pancreatic cancer, 3 of these patients had one previous chemotherapy regimen not containing either of the study drug combination. One patient, who had received experimental treatment with a polo-like kinase inhibitor previously showed a PR after the second cycle. Another 2 patients were stable. The median PFS of all patients with pancreatic cancer was 98 days.

Other patients who were evaluable for antitumor activity had a CUP syndrome or head-and-neck cancer. These patients experienced SD with a PFS of 272 and 191 days, respectively.

As there were only 12 subjects valid for efficacy analysis, it is difficult to draw reliable conclusions on the antitumor efficacy of the combination treatment of sorafenib with cisplatin and gemcitabine.

Discussion

This study was a phase IB study since pharmacokinetics and toxicity formed a major part of the investigation. However, since this was a preparation for a randomized phase III trial in NSCLC with efficacy as a major endpoint, we aimed at NSCLC patients as a major subgroup of our patients.

Sorafenib administered continuously as an oral treatment in combination with IV gemcitabine and cisplatin demonstrated an acceptable, although rather toxic safety profile. We did not observe unexpected toxicities, and the sorafenib-related adverse events (rash/hand-foot-syndrome and diarrhea) were consistent with earlier studies. No clinically relevant pharmacokinetic drug–drug interaction between sorafenib, cisplatin, and gemcitabine was detected. Clinical outcomes, pharmacokinetic, and safety data support the recommendation of 400 mg sorafenib twice daily in combination with cisplatin and gemcitabine to be further evaluated in clinical studies.

Recently, the results of Phase III data on sorafenib in combination with gemcitabine and cisplatin versus gemcitabine and cisplatin alone (i.e., placebo) in the first-line treatment of advanced NSCLC (NExUS-Trial: NSCLC research experience utilizing sorafenib) was announced [12]. Patients received up to 6 cycles chemotherapy, and thereafter, patients continued sorafenib or placebo until progression or intolerable toxicity. A total of 904 patients were randomized, but only patients with non-squamous cell carcinoma were included in the primary efficacy analyses. No overall survival benefit was demonstrated. However, statistically significant improvement of PFS (hazard ratio (HR) 0.83; 183 vs. 168 days; *P* value 0.008) and prolongation of time to progression (HR 0.73; *P* value 0.0004) were observed. The adverse event profile of the triple combination was generally acceptable and did not show any unexpected toxicities.

The combination of sorafenib with platinum-doublet chemotherapy did not confer overall survival benefit in unselected patients with advanced NSCLC, as has been reported also for the other tyrosine kinase inhibitors [13, 14]. However, large phase III trials have recently been published in patients with early, resectable NSCLC including studies of biomarkers identifying subsets of patients that benefited most from the experimental strategy, as has been reported for the IALT-bio study [15] or the IPASS study on EGFR tyrosine kinase inhibitor or platinum-based chemotherapy [16]. The BATTLE Trial (Biomarker-integrated approaches of targeted therapy for lung cancer elimination) enrolled NSCLC patients that were heavily pretreated with poor prognosis, based on biomarker analysis. This randomized phase II trial prospectively allocated patients to 4 treatment arms: sorafenib, erlotinib, vandetanib, or erlotinib plus bexarotene. Approximately 40% of 244 evaluable patients were treated with sorafenib. Results suggested the activity of monotherapy sorafenib in the EGFR wild-type NSCLC patient population, which includes both KRAS wild type and mutants. Furthermore, disease control after 8 weeks was achieved in 64% of sorafenib-treated patients with EGFR wild type [17]. The impact of sorafenib in patients with KRAS mutation may warrant further evaluation, especially due to controversial data having been published in this context [18, 19]. In conclusion, this Phase I study demonstrated that sorafenib can be combined with gemcitabine and cisplatin in selected patient populations able to tolerate intensive and potentially toxic treatment regimens.

References

1. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M, Cao Y, Shujath J, Gawlak S, Eveleigh D, Rowley B, Liu L, Adnane L, Lynch M, Auclair D, Taylor I, Gedrich R, Voznesensky A, Riedl B, Post LE, Bollag G, Trail PA (2004) 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 64(19):7099–7109. doi:10.1158/0008-5472.CAN-04-1443
2. Azzoli CG, Baker S Jr, Temin S, Pao W, Aliff T, Brahmer J, Johnson DH, Laskin JL, Masters G, Milton D, Nordquist L, Pfister DG, Piantadosi S, Schiller JH, Smith R, Smith TJ, Strawn JR, Trent D, Giaccone G (2009) American society of clinical oncology clinical

practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 27(36):6251–6266. doi:10.1200/JCO.2009.23.5622
3. D'Addario G, Fruh M, Reck M, Baumann P, Klepetko W, Felip E (2010) Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 21(Suppl 5):v116–v119. doi:10.1093/annonc/mdq189
4. Cardenal F, Lopez-Cabrerizo MP, Anton A, Alberola V, Massuti B, Carrato A, Barneto I, Lomas M, Garcia M, Lianes P, Montalar J, Vadell C, Gonzalez-Larriba JL, Nguyen B, Artal A, Rosell R (1999) Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 17(1):12–18
5. Crino L, Scagliotti GV, Ricci S, De Marinis F, Rinaldi M, Gridelli C, Ceribelli A, Bianco R, Marangolo M, Di Costanzo F, Sassi M, Barni S, Ravaioli A, Adamo V, Portalone L, Cruciani G, Masotti A, Ferrara G, Gozzelino F, Tonato M (1999) Gemcitabine and cisplatin versus mitomycin, ifosfamide, and cisplatin in advanced non-small-cell lung cancer: a randomized phase III study of the Italian lung cancer project. J Clin Oncol 17(11):3522–3530
6. Heinemann V, Quietzsch D, Gieseler F, Gonnermann M, Schonekas H, Rost A, Neuhaus H, Haag C, Clemens M, Heinrich B, Vehling-Kaiser U, Fuchs M, Fleckenstein D, Gesierich W, Uthgenannt D, Einsele H, Holstege A, Hinke A, Schalhorn A, Wilkowski R (2006) Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol 24(24):3946–3952. doi:10.1200/JCO.2005.05.1490
7. Sun S, Schiller JH, Spinola M, Minna JD (2007) New molecularly targeted therapies for lung cancer. J Clin Invest 117(10):2740–2750. doi:10.1172/JCI31809
8. Flaherty KT, Schiller J, Schuchter LM, Liu G, Tuveson DA, Redlinger M, Lathia C, Xia C, Petrenciuc O, Hingorani SR, Jacobetz MA, Van Belle PA, Elder D, Brose MS, Weber BL, Albertini MR, O'Dwyer PJ (2008) A phase I trial of the oral, multikinase inhibitor sorafenib in combination with carboplatin and paclitaxel. Clin Cancer Res 14(15):4836–4842. doi:10.1158/1078-0432.CCR-07-4123
9. Kupsch P, Henning BF, Passarge K, Richly H, Wiesemann K, Hilger RA, Scheulen ME, Christensen O, Brendel E, Schwartz B, Hofstra E, Voigtmann R, Seeber S, Strumberg D (2005) Results of a phase I trial of sorafenib (BAY 43–9006) in combination with oxaliplatin in patients with refractory solid tumors, including colorectal cancer. Clin Colorectal Cancer 5(3):188–196
10. CTCAE (2006) National Cancer Institute Common Terminology of Adverse Events v3.0. http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf
11. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) 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 92(3):205–216
12. Gatzemeier U, Eisen T, Santoro M, Pazzola A, Bennouna J, Liao M, Strauss UP, Montegriffo E, Ong TJ, Biesma B (2010) Sorafenib (S) + gemcitabine/cisplatin (GC) vs GC alone in the first-line treatment of advanced non-small cell lung cancer (NSCLC): phase III NSCLC research EXperience Utilizing Sorafenib (NExUS) trial. 35th ESMO Congress, Milan, Italy. Ann Oncol 21(Supplement 8):viii7 (abstract)
13. Scagliotti G, Novello S, von Pawel J, Reck M, Pereira JR, Thomas M, Abrao Miziara JE, Balint B, De Marinis F, Keller A, Aren O, Csollak M, Albert I, Barrios CH, Grossi F, Krzakowski M, Cupit L, Cihon F, Dimatteo S, Hanna N (2010) Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. J Clin Oncol 28(11):1835–1842. doi:10.1200/JCO.2009.26.1321
14. Scagliotti G, Govindan R (2010) Targeting angiogenesis with multitargeted tyrosine kinase inhibitors in the treatment of non-small cell lung cancer. Oncologist 15(5):436–446. doi:10.1634/theoncologist.2009-0225
15. Olaussen KA, Dunant A, Fouret P, Brambilla E, Andre F, Haddad V, Taranchon E, Filipits M, Pirker R, Popper HH, Stahel R, Sabatier L, Pignon JP, Tursz T, Le Chevalier T, Soria JC (2006) DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 355(10):983–991. doi:10.1056/NEJMoa060570
16. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M (2009) Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361(10):947–957. doi:10.1056/NEJMoa0810699
17. Kim ES, Herbst RS, Lee JJ, Blumenschein Jr GR, Tsao A, Alden CM, Tang X, Liu S, Stewart DJ, Heymach JV, Tran HT, Hicks ME, Erasmus J Jr, Gupta S, Powis G, Lippman SM, Wistuba II, Hong WK (2010) The BATTLE trial (biomarker-integrated approaches of targeted therapy for lung cancer elimination): personalizing therapy for lung cancer. Oral presentation at the plenary session of the AACR 101st Annual Meeting, Washington, USA
18. Smit EF, Dingemans AM, Thunnissen FB, Hochstenbach MM, van Suylen RJ, Postmus PE (2010) Sorafenib in patients with advanced non-small cell lung cancer that harbor K-ras mutations: a brief report. J Thorac Oncol 5(5):719–720. doi:10.1097/JTO.0b013e3181d86ebf01243894-201005000-00021[pii]
19. Kelly RJ, Rajan A, Force J, Keen C, Cao L, Yu Y, Choyke PL, Turkbey B, Raffeld M, Xi L, Steinberg SM, Wright JJ, Lopez-Chavez A, Kummar S, Guttierrez M, Giaccone G (2011) Evaluation of KRAS mutations, angiogenic biomarkers and DCE-MRI in patients with advanced non-small cell lung cancer receiving sorafenib. Clin Cancer Res. doi:10.1158/1078-0432.CCR-10-2331