Cancer Chemother Pharmacol (2008) 61:535–548
DOI 10.1007/s00280-007-0639-9

REVIEW

Safety and anti-tumor activity of sorafenib (Nexavar®) in combination with other anti-cancer agents: a review of clinical trials

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Received: 11 July 2007 / Accepted: 29 October 2007 / Published online: 17 November 2007

Abstract
Purpose Sorafenib (Nexavar®) is an oral multi-kinase inhibitor that inhibits Raf serine/threonine kinases and receptor tyrosine kinases involved in tumor growth and angiogenesis. Sorafenib has demonstrated preclinical and clinical activity against several tumor types, as a monotherapy and in combination with other anti-cancer agents.
Methods This review summarizes the safety, pharmacokinetics, and anti-tumor activity of sorafenib combined with other targeted agents or cytotoxics from a series of Phase I/II trials in approximately 600 patients with advanced solid tumors.
Results Sorafenib in combination with other agents was generally well tolerated, and most adverse events were mild to moderate in severity. Frequent drug-related toxicities were dermatologic, gastrointestinal, or constitutional. Most trials supported sorafenib 400 mg bid as the recommended dose for combination. Sorafenib generally had little effect on the pharmacokinetics of coadministered agents and vice versa. Preliminary anti-tumor activity was observed; overall disease control rates (partial response plus stable disease) ranged from 33 to 92%. Particularly promising activity was observed in patients with melanoma, hepatocellular carcinoma, and non-small-cell lung cancer receiving sorafenib plus paclitaxel/carboplatin, doxorubicin, and gefitinib, respectively.
Conclusions Sorafenib demonstrated a good safety profile and encouraging anti-tumor effects when coadministered with other agents in patients with advanced solid tumors.

Keywords Combination · Chemotherapy · Phase I/II clinical trials · Solid tumors · Sorafenib · Targeted agent

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Introduction

Dysregulation of the Raf/MEK/ERK pathway, which is involved in cellular proliferation, survival, and differentiation, is implicated in the development of solid tumors [1] and is therefore a logical strategy for inhibiting malignant tumor cell proliferation and survival. The oral multi-kinase inhibitor sorafenib (Nexavar®; Bayer Pharmaceuticals Corporation, Onyx Pharmaceuticals) targets the Raf serine/threonine kinases (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 [2].

In Phase II/III clinical trials, single-agent sorafenib significantly prolonged progression-free survival (PFS) two to fourfold versus placebo in patients with advanced renal cell carcinoma (RCC), a historically chemoresistant tumor with a particularly poor prognosis [3, 4]. Furthermore, sorafenib treatment was associated with an estimated 28% reduction in mortality risk over placebo ($P = 0.018$; hazard ratio: 0.72) in the first survival analysis of a large, randomized, controlled Phase III trial in RCC [3]. Compared with standard chemotherapies that are associated with alopecia, anemia, neutropenia, renal or neurologic side-effects, single-agent sorafenib at 400 mg twice daily (bid) was found to be generally well tolerated throughout the Phase I–III clinical

trial program [3–6]. The majority of adverse events was mild to moderate in severity, followed a predictable course, and was manageable [3–6]. The most frequently reported drug-related adverse events were dermatologic [hand–foot skin reaction (HFSR), rash/desquamation], gastrointestinal (diarrhea), and constitutional (fatigue) [3, 5, 6]. Severe biochemical abnormalities, myelosuppression, hematologic, cardiovascular, hepatic, and renal toxicities were rarely reported [5]. Across the clinical program, treatment-emergent hypertension at any grade was observed in 5–17% (<5% at grade 3 or 4) of patients receiving sorafenib 400 mg bid [3, 5]. However, hypertension was manageable with interventional anti-hypertensive drugs [3]. Similarly, although dermatologic adverse events occurred in just over twice as many patients receiving sorafenib compared with those on placebo, these toxicities were generally reversible and resolvable with topical therapies, dose modification, or treatment interruption [3]. The excellent tolerability profile of sorafenib suggests that it could be combined with other anti-tumor agents, including cytotoxic agents that are usually associated with higher levels of toxicities, as well as other targeted therapies [7]. Evidence from several human tumor xenograft models suggests that the anti-tumor activity of a wide variety of chemotherapeutic agents, including doxorubicin, paclitaxel, cisplatin, docetaxel, and gemcitabine, is enhanced by concomitant inhibition of Raf expression [8, 9].

Combinatorial targeting of multiple points upstream and downstream in several signaling pathways is important for inhibition of tumor proliferation and induction of apoptosis, and thus provides a rationale for combining sorafenib with other targeted agents. Furthermore, combining drugs that have different mechanisms of action may enhance anti-tumor activity by overcoming mechanisms of drug resistance [10]. Preliminary preclinical studies with sorafenib in combination with gefitinib, vinorelbine, gemcitabine, and irinotecan have not demonstrated a significant increase in toxicity above that expected for either agent alone [11, 12]. Sorafenib did not abrogate the anti-tumor activity of coadministered gefitinib or vinorelbine in non-small-cell lung cancer (NSCLC) xenograft models [11]. In a colon tumor xenograft model, sorafenib plus irinotecan did not produce greater toxicity than expected for either agent alone, and did not reduce the efficacy of irinotecan [12]. Contrastingly, dose reductions of both sorafenib and doxorubicin were required for concomitant administration of these agents in a breast xenograft model [11].

Based on these data, a series of dose-ranging trials was undertaken to assess the safety, pharmacokinetics, and anti-tumor activity of sorafenib in combination with anti-cancer agents, including chemotherapies, immunotherapies, and other targeted agents. A review of these data from sorafenib combination trials is provided.

Sorafenib combination with anti-cancer therapies

Data are available from 19 Phase I/II open-label, uncontrolled clinical trials conducted in over 600 patients investigating sorafenib in combination with other agents (Table 1). In general, Phase I studies consisted of a dose-escalation part in patients with refractory solid tumors followed by an extension part, administering the maximum tolerated dose (MTD) to patients with a specific tumor type.

Safety

Dose-limiting toxicities

Common dose-limiting toxicities (DLTs) were HFSR and diarrhea, and these generally occurred at higher dose levels (Table 2) [13–17]. Less-frequent DLTs consisted of fatigue [18], hyperuricemia [17], rash [19], and asthenia [20]. The MTD was not reached in many of the combination trials [13, 14, 16–18, 20–22]. With the exception of the bevacizumab combination [23, 24], trials generally supported a dosing schedule of continuous oral sorafenib 400 mg bid. Sorafenib 200 mg bid plus bevacizumab 5 mg/kg was the MTD [23, 24]; dose-limiting hypertension, proteinuria, thrombocytopenia, and elevated lipase were reported in patients receiving sorafenib plus bevacizumab 10 mg/kg [23, 24]. In the trials in which full doses of both agents could be administered without reaching the MTD, the most frequently reported DLTs were dermatologic and gastrointestinal symptoms. Five of 22 patients (23%) receiving sorafenib 400 mg bid plus doxorubicin experienced reversible dose-limiting HFSR that was considered sorafenib related [14]. Two patients (10%) in the hepatocellular carcinoma (HCC) extension cohort receiving sorafenib plus doxorubicin had sorafenib-related dose-limiting HFSR that resolved after dose reduction or temporary treatment discontinuation [13]. Only one of seven patients (14%) receiving sorafenib (400 mg bid) and gemcitabine (1,000 mg/m^2) developed grade 3 fatigue that was dose limiting [18]. None of the other 19 patients in the dose-escalation phase or the 23 patients in the pancreatic extension cohort had DLTs [18]. Only two DLTs of sorafenib-related grade 3 diarrhea occurred in two patients (5%) who received the 400 mg bid dose, in combination with oxaliplatin [16]. Furthermore, only one DLT (grade 3 asthenia) was observed in one patient (8%) receiving sorafenib (400 mg bid) plus interferon-α2a (9 MIU three-times weekly) [20]. In melanoma patients, only one DLT (grade 3 HFSR) was reported out of a total of 15 patients receiving sorafenib (400 mg bid) plus dacarbazine (DTIC) (1,000 mg/m^2) [15]. Only two DLTs were reported with sorafenib plus erlotinib (grade 3 hypophosphatemia and grade 2 diarrhea/anorexia) and,

Table 1 Combination trial details

First author, date	Patients (*n*)	Tumor type	Duration of each combination treatment cycle	Doses of combination treatment regimens	
				Other anticancer agent	Sorafenib (bid)
Kupsch 2005 [16]					
Dose escalation	27	Refractory solid tumors	3 weeks	Oxaliplatin 130 mg/m^2 on Day 1	Sorafenib 200 or 400 mg from Day 4
Extension	10	Oxaliplatin-refractory (i.e. pretreated) CRC	3 weeks	Oxaliplatin 130 mg/m^2 on Day 1	Sorafenib 400 mg from Day 4
Richly 2004/2006 [13, 14]					
Dose escalation	34	Refractory solid tumors	3 weeks	Doxorubicin 60 mg/m^2 on Day 1	Sorafenib 100, 200, or 400 mg on Day 4
Extension	20	Advanced, refractory HCC	3 weeks	Doxorubicin 60 mg/m^2 on Day 1	Sorafenib 400 mg bid on Day 4
Flaherty 2003/2004/2006 [19, 26, 33]					
Dose escalation	11	Refractory solid tumors	3 weeks	Carboplatin AUC 6 and paclitaxel 225 mg/m^2 on Day 1 (3-h i.v. infusion)	Sorafenib 100, 200, or 400 mg on Days 2–19
Melanoma cohort	35	Progressive metastatic melanoma	3 weeks	Carboplatin AUC 6 and paclitaxel 225 mg/m^2 on Day 1 (3-h i.v. infusion)	Sorafenib 100, 200, or 400 mg on Days 2–19
Melanoma cohort	105	Metastatic melanoma	3 weeks	Carboplatin AUC 6 and paclitaxel 225 mg/m^2 on Day 1 (3-h i.v. infusion)	Sorafenib 100, 200, or 400 mg on Days 2–19
Schiller 2006 [27]					
NSCLC cohort	15	Advanced NSCLC	3 weeks	Carboplatin AUC 6 and paclitaxel 225 mg/m^2 on Day 1 (3-h i.v. infusion)	Sorafenib 100, 200, or 400 mg on Days 2–19
Siu 2006 [18]					
Dose escalation	19	Refractory solid tumors	Cycle 1:8 weeks	Gemcitabine 1,000 mg/m^2 once weekly (except Week 8)	Sorafenib 100, 200, or 400 mg initiated on Day 2 and administered continuously thereafter
			Cycle 2:4 weeks	Gemcitabine 1,000 mg/m^2 once weekly (except Week 4)	
Extension	23	Advanced pancreatic cancer	Cycle 1:8 weeks	Gemcitabine 1,000 mg/m^2 once weekly (except Week 8)	Sorafenib 400 mg initiated on Day 2 and administered continuously thereafter
			Cycle 2:4 weeks	Gemcitabine 1,000 mg/m^2 once weekly (except Week 4)	
Steinbild 2005 [22]					
Dose escalation	20	Advanced, refractory solid tumors	6 weeks (4 weeks on, 2 weeks off)	Irinotecan 125 mg/m^2 once weekly administered on Days 1, 8, 15, and 22 of each cycle (2-week treatment break at end of each cycle)	Continuous sorafenib 100, 200, or 400 mg
Extension	12	Advanced, refractory CRC	6 weeks (4 weeks on, 2 weeks off)	Irinotecan 140 mg (fixed dose) once weekly administered on Days 1, 8, 15, and 22 of each cycle (2-week treatment break at end of each cycle)	Continuous sorafenib 400 mg

Table 1 continued

First author, date	Patients (*n*)	Tumor type	Duration of each combination treatment cycle	Doses of combination treatment regimens	
				Other anticancer agent	Sorafenib (bid)
Figer 2004 [17]	24	Solid tumors eligible for treatment with LCV/5-FU	2 weeks	Day 1: infusion of LCV 400 mg/m^2 over 2 h, followed by infusion of 5-FU 400 mg/m^2 bolus and 2,400 mg/m^2 infusion over 46 h	Continuous sorafenib 100, 200, or 400 mg initiated after the first LCV/5-FU dose
Eisen 2005 [15]	18	Metastatic melanoma	3 weeks	Day 1: DTIC 1,000 mg/m^2	Continuous sorafenib 200 or 400 mg
Adjei 2005 [21]	32	Unresectable/recurrent advanced NSCLC	Continuous administration	Gefitinib 250 mg once daily	Sorafenib 200 or 400 mg
Robert 2005 [20]	13	Metastatic RCC or malignant melanoma	4 weeks	Interferon-α2a 6 or 9 MIU, three-times weekly	Continuous sorafenib 200 or 400 mg
Posadas 2005 [24]	12	Refractory solid tumors	2 weeks	One dose of bevacizumab 5 or 10 mg/kg	Continuous sorafenib 200 mg
Azad 2006 [23]	34	Advanced solid tumors	4 weeks	Bevacizumab 5 mg/kg once every 2 weeks or 10 mg/kg once every 2 weeks	Continuous sorafenib 200 mg or 400 mg
Sosman 2006 [51]	18	Metastatic RCC	4 weeks	Bevacizumab 5–10 mg/kg once every 2 weeks	200–400 mg
Lorigan 2006 [28]	30	Metastatic melanoma	3 weeks	DTIC 1000 mg/m^2 on Day 1 of every cycle	Continuous sorafenib 400 mg bid
Welch 2006 [35]	26	Recurrent, epithelial ovarian cancer	Cycle 1:8 weeks Subsequent Cycles: 4 weeks	7 weeks of gemcitabine (1,000 mg/m^2 i.v.) weekly (Cycle 1), followed by 1-week break; then 3 weeks of gemcitabine in each 4-week cycle	Continuous sorafenib 400 mg
Amaravadi 2006 [30]	58	Advanced melanoma	4–8 weeks	Oral temozolomide 75 mg/m^2 for 6/8 weeks (Arm A) or 150 mg/m^2, once daily, Days 1–5/28 (Arm B)	Continuous sorafenib 400 mg
Ryan 2006 [32]	58	First-line, advanced RCC	–	Interferon-α2b 10 MIU, s.c., three-times weekly	Continuous sorafenib 400 mg
Gollob 2006 [31]	31	First- or second-line (excluding interferon-α-treated patients), metastatic RCC	8 weeks	Interferon-α2b 10 MIU, s.c., three-times weekly	Continuous sorafenib 400 mg
Duran 2006 [25]	17	Advanced solid tumors	4 weeks	Erlotinib 100 or 150 mg qd	Continuous sorafenib 200 or 400 mg

5-FU 5-Fluorouracil, *bid* twice daily, *CRC* colorectal cancer, *HCC* hepatocellular carcinoma, *LCV* leucovorin, *MIU* million international units, *NSCLC* non-small-cell lung cancer, *qd* every day, *RCC* renal cell carcinoma

therefore, the recommended dose of this combination was sorafenib 400 mg bid plus erlotinib 150 mg qd (Table 2) [25].

Adverse event profiles

The sorafenib combination studies were generally well tolerated; in most studies, tolerability profiles were similar to those expected with each agent as a monotherapy [15–18, 25–28]. Only sorafenib in combination with the monoclonal antibody against VEGF, bevacizumab, was associated with greater than expected toxicity based on the safety profile of the individual agents [23, 24]. This combination appeared to increase the toxicity above that reported for the single agents. The most common adverse events with sorafenib 200 mg bid plus bevacizumab 5 mg/kg were hypertension, HFSR, leukopenia and infection. All patients had elevated alanine aminotranferease (ALT) and aspartate aminotransferase (AST), rhinorrhea, fatigue, anorexia, weight loss, and neuropathy at grade 1 or 2 [23, 24]. In the majority of other trials, frequent drug-related adverse events were dermatologic (HFSR, rash/desquamation, and alopecia), gastrointestinal (diarrhea and nausea), or constitutional (fatigue) and most were grade 1 or 2 in severity. The overall incidence of grade 1 or 2 HFSR was greater (approximately 50 vs. 25%) in patients receiving sorafenib 400 mg bid versus 200 mg bid when combined with gefitinib, oxaliplatin, doxorubicin, or DTIC [14–16, 21]. The most common grade 3 or 4 drug-related adverse events were dermatologic (HFSR, rash/desquamation) and gastrointestinal toxicities (diarrhea, vomiting), which are typical of sorafenib, or bone marrow suppression (neutrophils/granulocytes/leukocytes and febrile neutropenia), which is commonly associated with standard chemotherapy.

Importantly, the adverse events observed in these combination trials with cytotoxic chemotherapy rarely overlapped with those more commonly associated with sorafenib. High-dose docetaxel is associated with neutrophil- and leukocyte-related toxicities [29]. In patients with advanced melanoma receiving sorafenib plus temozolomide, the majority of toxicities could be attributed to either therapy [30], whereas increases in the incidence of constitutional and gastrointestinal toxicities in interferon-α2b combination studies were typical of interferon-α2b treatment [31, 32]. Together, these studies suggest that sorafenib has the potential to be combined with a variety of chemotherapies and targeted agents.

Pharmacokinetics

Sorafenib generally had little effect on the pharmacokinetics of coadministered agents and vice versa (Table 3) [16–18, 20, 33]. Increases were observed in drug exposures of doxorubicin, irinotecan, and docetaxel, in combination with sorafenib [13, 14, 22]. These findings were neither generally dose related nor were they associated with increased clinical toxicity, and thus were not considered clinically meaningful. Although sorafenib pharmacokinetics were not influenced significantly by concomitant doxorubicin, slight increases in doxorubicin and doxorubicinol C_{max} and AUC values were observed with sorafenib 400 mg bid (given as 50 mg tablets) [13, 14], but these alterations were not associated with an increase in myelosuppression. No significant change in doxorubicin exposure was observed when coadministered with either sorafenib 400 mg bid given as 200 mg tablets, or with lower doses of sorafenib (100 or 200 mg bid) [13, 14]. Coadministration of sorafenib (100 or 200 mg bid) and irinotecan (125 mg/m^2) did not substantially alter the clinical tolerability of either drug. Increased exposure to irinotecan and its metabolite SN-38 was reported with the combination of irinotecan 125 mg/m^2 or 140 mg (fixed dose) with sorafenib 400 mg bid, but did not appear to increase clinical toxicity, suggesting that this is not a clinically significant effect. Irinotecan 140 mg (fixed dose) had a negligible effect on the pharmacokinetics of sorafenib [22].

Efficacy

Anti-tumor activity

Anti-tumor activity for mixed-tumor studies and single-tumor studies are presented in Tables 4 and 5, respectively. Overall disease control rates (partial response plus stable disease) ranged from 33 to 92% across these trials. Sorafenib plus paclitaxel/carboplatin showed particularly promising activity in metastatic melanoma patients: one (∼1%) complete response, a partial response rate of 26%, and a stable disease rate of 58% (disease control rate of 84%) were reported [26]. In addition, 13–17% of melanoma patients achieved a partial response and 53–61% of patients had stable disease (disease control rate of 66–78%) with sorafenib in combination with DTIC [15, 28]. Although few trials in advanced melanoma describe PFS, the median PFS of 8.8 months reported with sorafenib plus carboplatin/paclitaxel compares favorably with that reported for DTIC/cisplatin/interferon-α2a with or without interleukin-2 (3.9 and 3.0 months, respectively) [26, 34]. In a subpopulation of NSCLC patients, sorafenib plus carboplatin/paclitaxel also demonstrated a relatively high level of partial responses and disease stabilizations (27 and 47%, respectively), as well as a median PFS of almost 5 months [27]. The combination of sorafenib and doxorubicin appeared promising in advanced HCC, with 67% of patients in an

Table 2 Dose-limiting toxicities and maximum tolerated doses

First author, date	Patients (*n*)	Combination treatment arm		Dose-limiting toxicity	Maximum tolerated dose
		Sorafenib bid	Other anticancer agent		
Kupsch 2005 [16]	8	200 mg	Oxaliplatin	None	Not reached. Recommended dose: sorafenib 400 mg bid + oxaliplatin 130 mg/m^2
	8	400 mg (50 mg tablets)	Oxaliplatin	None	
	11	400 mg (200 mg tablets)	Oxaliplatin	1 patient: grade 3 diarrhea	
	10	400 mg	Oxaliplatin-extension	1 patient: grade 3 diarrhea	
Richly 2004/2006 [13, 14]	6	100 mg (50 mg tablets)	Doxorubicin	None	Not reached. Recommended dose: sorafenib 400 mg bid + doxorubicin 60 mg/m^2
	6	200 mg	Doxorubicin	None	
	12	400 mg (50 mg tablets)	Doxorubicin	3 patients: HFSR	
	10	400 mg (200 mg tablets)	Doxorubicin	2 patients: HFSR	
	20	400 mg	Doxorubicin-extension	2 patients: HFSR	
Flaherty 2003/2004/2006 [19, 26, 33]	7	100 mg	Carboplatin/paclitaxel	1 patient: grade 3 rash	TBC
	3	200 mg	Carboplatin/paclitaxel	None	
	1	400 mg	Carboplatin/paclitaxel	None	
	35	100, 200, or 400 mg	Carboplatin/paclitaxel-melanoma cohort	TBC	TBC
	105	100, 200, or 400 mg	Carboplatin/paclitaxel-melanoma cohort	TBC	TBC
Schiller 2006 [27]	15	100, 200, or 400 mg	Carboplatin/paclitaxel-NSCLC substudy	Not reported	Not reported
Siu 2006 [18]	3	100 mg	Gemcitabine	None	Not reached. Recommended dose: sorafenib 400 mg bid + gemcitabine 1,000 mg/m^2
	3	200 mg	Gemcitabine	None	
	7	400 mg (50 mg tablets)	Gemcitabine	1 patient: grade 3 fatigue	
	6	400 mg (200 mg tablets)	Gemcitabine	None	
	23	400 mg	Gemcitabine-extension	None	
Steinbild 2005 [22]	20	100, 200, or 400 mg	Irinotecan 125 mg/m^2	Not reported	Not reached
	12	400 mg	Irinotecan 140 mg (fixed dose)	Not reported	
Figer 2004 [17]	10	100 mg	LCV/5-FU	1 patient: grade 4 hyperuricemia	Not reached. Recommended dose: sorafenib 400 mg bid + LCV/5-FU
	8	200 mg	LCV/5-FU	None	
	6	400 mg	LCV/5-FU	1 patient: grade 3 diarrhea	
Eisen 2005 [15]	3	200 mg	DTIC	None	Sorafenib 400 mg bid + DTIC 1000 mg/m^2
	15	400 mg	DTIC	1 patient: grade 3 HFSR	
Adjei 2005 [21]	9	200 mg	Gefitinib	Not reported	Not reached. Recommended dose: sorafenib 400 mg bid + gefitinib 250 mg bid continuously
	23	400 mg	Gefitinib	Not reported	
Robert 2005 [20]	4	200 mg bid	IFN-α2a 6 MIU	None	Not reached
	3	400 mg bid	IFN-α2a 6 MIU	None	
	6	400 mg bid	IFN-α2a 9 MIU	1 patient: grade 3 asthenia	

Table 2 continued

First author, date	Patients (*n*)	Combination treatment arm		Dose-limiting toxicity	Maximum tolerated dose
		Sorafenib bid	Other anticancer agent		
Posadas 2005 [24]	TBC	200 mg bid	Bevacizumab 5 mg/kg	None	Sorafenib 200 mg bid + bevacizumab 5 mg/kg
	TBC	200 mg bid	Bevacizumab 10 mg/kg	Hypertension, HFSR, fatigue, diarrhea, elevated lipase, proteinuria, and thrombocytopenia	
Azad 2006 [23]	34	200 mg bid	Bevacizumab 5 mg/kg or 10 mg/kg	2 patients: grade 3 proteinuria; 3 patients: grade 3 hypertension	Sorafenib 200 mg bid + bevacizumab 5 mg/kg
Sosman 2006 [51]	18	200–400 mg	Bevacizumab 5–10 mg/kg	2 patients: grade 3 HFSR	TBC
Lorigan 2006 [28]	30	400 mg	DTIC 1,000 mg/m^2	Not reported	Not reported
Welch 2006 [35]	26	400 mg	Gemcitabine 1,000 mg/m^2	Not reported	Not reported
Amaravadi 2006 [30]	65	400 mg	Temozolomide 75–150 mg/m^2	Not reported	Not reported
Ryan 2006 [32]	58	400 mg	IFN-α2b 10 MIU	Not reported	Not reported
Gollob 2006 [31]	31	400 mg	IFN-α2b 10 MIU	Not reported	Not reported
Duran 2006 [25]	17	200 or 400 mg	Erlotinib 100 or 150 mg qd	1 patient: grade 3 hypophosphatemia; 1 patient: grade 2 intolerable diarrhea and anorexia	Not reported

5-FU 5-Fluorouracil, *bid* twice daily, *DTIC* dacarbazine, *HFSR* hand–foot skin reaction, *IFN* interferon, *LCV* leucovorin, *MIU* million international units, *NSCLC* non-small-cell lung cancer, *qd* every day, *TBC* to be confirmed

Table 3 Pharmacokinetics (note: trials in which pharmacokinetics were not measured have been omitted)

First author, date	Treatment	Effect of sorafenib on concomitant agent	Effect of concomitant agent on sorafenib
Kupsch 2005 [16]	Sorafenib + oxaliplatin	Small increase in total platinum: C_{max} changed by factors of 0.87–1.43, and AUC_{0-48} by 1.12–1.21 No clear effect on unbound platinum: C_{max} changed by factors of 0.74–1.55, and AUC_{0-48} by 0.91–1.09 MTD not reached; no clear toxicity relationship found	Oxaliplatin had clear dose-related effect on sorafenib exposure Affected C_{max} by factors of 0.95–1.36 Affected AUC_{0-8} by factors of 0.91–1.41
Richly 2006 [13, 14]	Sorafenib + doxorubicin	Dose escalation: exposure increased with sorafenib 400 mg bid (50 mg tablets) only –Affected C_{max} for doxorubicin by factors of 0.74–2.03, and AUC_{0-8} by 0.85–1.47 –Affected C_{max} for doxorubicinol by factors of 0.93–1.30, and AUC_{0-8} by 0.91–1.20 Extension: increase in exposure observed, by a factor of 1.34 for C_{max} and 1.21 for AUC_{0-8} Increased doxorubicin exposure was not associated with increased clinical toxicity (no change in myelosuppression)	Dose escalation: –Affected C_{max} by factors of 0.94–1.26 – Affected AUC_{0-8} by factors of 1.01–1.36 Extension: no effect
Flaherty 2004 [33]	Sorafenib + carboplatin/paclitaxel	No consistent increase in exposure of paclitaxel, 6-hydroxy paclitaxel, total, or unbound platinum with increasing sorafenib dose or from treatment Cycle 1 to 2	Not reported
Siu 2006 [18]	Sorafenib + gemcitabine	Slightly decreased gemcitabine exposure observed in pancreatic extension (not statistically significant) –Affected C_{max} for gemcitabine by factors of 0.69–2.46 –Affected C_{max} for dFdU by factors of 1.01–1.13	No direct evidence that sorafenib pharmacokinetics was altered by gemcitabine; trend towards decreased exposure in pancreatic extension (not statistically significant) – Affected C_{max} by factors of 0.76–1.11 – Affected AUC by factor of 0.59–0.98
Steinbild 2005 [22]	Sorafenib + irinotecan	100 or 200 mg bid had no effect 400 mg bid increased exposure to irinotecan and metabolite SN 38 but without increasing clinical toxicity	Irinotecan 125 mg/m^2 and 140 mg (fixed dose) had no effect
Figer 2004 [17]	Sorafenib + LCV/5-FU	Moderate increase in 5-FU exposure only at lowest dose (100 mg bid)	No clear dose-related increase in exposure
Robert 2005 [20]	Sorafenib + IFN-α2a	Not reported	No significant effect

5-FU 5-Fluorouracil, *bid* twice daily, *dFdU* 2',2'-difluoro-2'-deoxyuridine, *IFN* interferon, *LCV* leucovorin, *MTD* maximum tolerated dose

extension cohort achieving stable disease [13]. Partial responses were reported in two heavily pretreated ovarian cancer patients (11%) treated with sorafenib (400 mg bid cohort) plus gemcitabine in the dose-escalation part of the trial. Both patients had received previous taxane, platinum, and anthracycline therapies [18]. A relatively high level of disease stabilization was achieved with sorafenib plus gemcitabine in the dose-escalation phase in patients with mixed solid tumors and in the MTD expansion cohort in patients with pancreatic cancer (63 and 57%, respectively) [18]. This combination demonstrated anti-tumor activity in a recent Phase II study in epithelial ovarian cancer patients, with approximately two-thirds of patients achieving partial response or stable disease, and a median time to progression of 7.6 months [35]. Sorafenib combined with the epidermal growth factor receptor (EGFR) inhibitor gefitinib demonstrated encouraging anti-tumor activity in NSCLC patients, with 63% achieving stable disease (median duration 20.4 weeks) (Table 5) [21]. Similarly, sorafenib plus another EGFR inhibitor, erlotinib, produced partial responses in 23% of patients and stable disease in 62% [25]. A relatively high disease stabilization rate (42–75%) was also reported in patients with solid tumors who received sorafenib combined with bevacizumab (Table 4) [23, 24]. Four of 14 patients with epithelial ovarian cancer achieved partial responses with sorafenib plus bevacizumab [23]. Fistula formation was observed in areas of rapid tumor regression in three ovarian cancer patients, two of whom achieved partial response [23]. In metastatic RCC patients in the first- and second-line setting, sorafenib plus interferon-α2b generated response rates that were greater than either agent alone: two complete responses were reported and approximately one third of patients achieved partial response [31, 32].

Discussion

Sorafenib in combination was generally safe and well tolerated in patients with advanced, progressive solid tumors, including RCC, melanoma, HCC, and colorectal cancer (CRC), with little evidence of clinically relevant drug–drug interactions. The reported safety and tolerability profiles associated with sorafenib in combination with other anticancer agents are encouraging and consistent with the results of the preclinical combination studies [11, 12].

The safety profile observed in the Phase I/II combination trials was similar to that reported in Phase I trials of single-agent sorafenib [36]. The most frequently observed adverse events included HFSR, rash, diarrhea, and fatigue, which were mostly mild to moderate in severity, and most tended to occur at higher doses of sorafenib. In a pooled safety analysis from four Phase I trials, the occurrence of skin toxicity or diarrhea in patients receiving sorafenib at doses ranging 300–600 mg bid is correlated with a longer time to tumor progression [36]. The optimal dose of sorafenib plus bevacizumab has yet to be established. Potential synergistic inhibitory effects on the VEGF/VEGFR pathway may be responsible for the apparent increased level of toxicities (e.g. hypertension, proteinuria, and thrombocytopenia), observed with sorafenib plus bevacizumab, above those reported for at least equal doses of single agents [23, 24]. Despite this, sorafenib appears to be easily combined with many other treatments due to its favorable safety profile on a continuous administration schedule and its convenient oral route of administration.

Generally, there were no clinically relevant pharmacokinetic drug–drug interactions when sorafenib was combined with other anti-cancer agents. Exposure to doxorubicin, irinotecan, and docetaxel did increase when combined with sorafenib; however, this effect was not accompanied by any significant increase in clinical toxicity. Interactions at the level of hepatic metabolism and elimination may account for the observed increase in drug exposure of these agents.

Multiple signaling pathways contribute to tumor growth and angiogenesis. Therefore, combining agents with different mechanisms of action may enhance anti-tumor activity through horizontal and/or vertical inhibition of multiple tumorigenic pathways [37]. For example, sorafenib plus an EGFR inhibitor (e.g. erlotinib or gefitinib) may achieve vertical inhibition of the Raf/MEK/ERK pathway by targeting both Raf and the EGFR in tumor cells. A horizontal inhibition of signaling pathways may be achieved through inhibition of Raf, PDGFR, and VEGFR with sorafenib and the anti-VEGF monoclonal antibody bevacizumab.

Drug resistance to cytotoxics, such as doxorubicin and docetaxel, is a common clinical problem limiting their effectiveness, especially as single agents. Data suggest that conventional therapies exert their cytotoxic activities primarily by inducing apoptosis in tumor cells, and that resistant cells adopt mechanisms to evade apoptotic pathways [38]. One mechanism of chemoresistance may involve the overexpression of anti-apoptotic molecules, such as Bcl-2 [39]. Recent evidence suggests that synergism between Bcl-2 and Raf-1 may enhance the suppression of apoptosis [39]. Sorafenib can induce apoptosis in vitro in a variety of human cancer cell lines by enhancing the proteasomal degradation of Bcl-2 family member, Mcl-1 [40]. Thus, down-regulation of anti-apoptotic molecules may help sensitize tumor cells to chemotherapy. Expression of the multidrug resistance 1 (*mdr-1*) gene is associated with solid tumors that have a high level of intrinsic or acquired chemoresistance [41]. The effects of Raf in regulating the *mdr-1* gene and on regulating the sensitivity of tumor cells to chemotherapy-induced cell death suggest that drug resistance may be reduced with a Raf inhibitor, such as sorafenib [42].

Table 4 Anti-tumor effects: mixed-tumor-type studies

First author, date	Treatment	Patients, *n*	Tumor type: partial response (*n*; %)	Tumor type: Stable disease (*n*; %)	Other clinical endpoints
Kupsch 2005 [16]	Sorafenib 200/400 mg bid + oxaliplatin (dose escalation)	32[a]	Gastric cancer (2; 6)	Types not specified (17; 53)	TTP range 76–452 days
Richly 2004/ 2006 [13, 14]	Sorafenib 100/200/400 mg bid + doxorubicin (dose escalation)	31[a]	Pleural mesothelioma (1; 3)	HCC (4) Pancreas (3) RCC (2) Breast (1) Lung (1) Colon (1) Other (3) Total (15; 48)	–
Flaherty 2003/2004 [19, 33]	Sorafenib 100/200/400 mg bid + carboplatin/paclitaxel (dose escalation)	11	Melanoma (2; 18)[b]	Basal cell carcinoma (1) Melanoma (1) Sarcoma (1) RCC (1) Total (4; 36)[c]	–
Siu 2006 [18]	Sorafenib 100/200/400 mg bid + gemcitabine	19	Ovary (2; 11)	Types not specified Total (12; 63)	–
Steinbild 2005 [22]	Sorafenib 100/200/400 mg bid + irinotecan	32[a]	0 (0)	Types not specified Total (17; 63)	–
Figer 2004 [17]	Sorafenib 100/200/400 mg bid + LCV/5-FU	24	Types not specifiedTotal (2; 8)	Types not specified Total (6; 25)[d]	–
Robert 2005 [20]	Sorafenib 200/400 mg bid + IFN-α2a 6/9 MIU	13[a]	RCC (1; 8)	RCC (7) Melanoma (1) Total (8; 67)	–
Posadas 2005 [24]	Sorafenib 200 mg bid + bevacizumab 5/10 mg/kg	12	Ovary (2; 17)	Types not specified Total (9; 75)	–
Azad 2006 [23]	Sorafenib 200 mg bid + bevacizumab 5/10 mg/kg	34[a]	Ovary (4; 11)	Ovary (3) RCC (3) Melanoma (3) Colon (3) Sarcoma (2) Other (2) Total (16; 42)	Rapid tumor regression with fistula formation in 3 ovarian cancer patients (2 of these achieved partial response) DCE-MRI and FDG-PET showed reduced vascularity with therapy
Duran 2006 [25]	Sorafenib 200/400 mg bid + erlotinib 100/150 mg qd	13[a]	Cholangiocarcinoma (1; 8) Neuroendocrine (1; 8) Small bowel adenocarcinoma (1; 8)	Types not specified Total (8; 62)	–

5-FU 5-Fluorouracil, *bid* twice daily, *DCE-MRI* dynamic contrast-enhanced magnetic resonance imaging, *FDG-PET*, fluorodeoxyglucose-positron emission tomography, *HCC* hepatocellular carcinoma, *IFN* interferon, *LCV* leucovorin, *MIU* million international units, *RCC* renal cell cancer, *TTP* time to progression

[a] Not all patients were evaluable for response

[b] Unconfirmed responses

[c] Including one minor response

[d] Including two minor responses

Table 5 Anti-tumor effects: single-tumor-type studies/cohorts

First author, date	Tumor type	Treatment	Patients, *n*	Partial response, *n* (%)	Stable disease, *n* (%)	Other responses and clinical endpoints, *n* (%)
Kupsch 2005 [16]	Oxaliplatin-refractory CRC	Sorafenib 200/400 mg bid + oxaliplatin (dose escalation)	9[a]	0 (0)	7 (78)	
Richly 2004/ 2006 [13, 14]	Advanced, refractory HCC	Sorafenib 400 mg bid plus doxorubicin (extension)	18[a]	1 (6)	12 (67)	–
Flaherty 2006 [26]	Progressive metastatic melanoma	Sorafenib 100/200/400 mg bid + carboplatin/paclitaxel (melanoma cohort)	105	27 (26)plus 1 (∼1%) complete response	61 (58)	Median TTP 8.8 months
Schiller 2006 [27]	Advanced NSCLC	Sorafenib 100/200/400 mg bid + carboplatin/paclitaxel	15[a]	4 (27)	7 (47)	Median PFS 34 weeks; median duration of response ∼25 weeks
Siu 2006 [18]	Pancreatic cancer cohort	Sorafenib 400 mg bid + gemcitabine 1000 mg/m^2	23	0 (0)	13 (57)	
Steinbild 2005 [22]	Advanced, refractory CRC	Sorafenib 400 mg bid + irinotecan	7[a]	0 (0)	5 (71)	
Eisen 2005 [15]	Metastatic melanoma	Sorafenib 200/400 mg bid + DTIC	18	3 (17)	11 (61)	Median PFS 23 weeks at 200 mg, 13 weeks at 400 mg
Lorigan 2006 [28]	Metastatic melanoma	Sorafenib 400 mg bid + DTIC	30[a]	5 (16.7)	13 (43.3)	Median duration of partial response 162 days; duration of SD 104 days; median PFS 3.7 months; median overall survival 9.3 months
Adjei 2005 [21]	Unresectable/ recurrent advanced NSCLC	Sorafenib 200/400 mg bid + gefitinib	32	1 (3)	20 (63)	Median PFS 18 weeks
Sosman 2006 [51]	Metastatic RCC	Sorafenib 200/400 mg bid + bevacizumab 5/10 mg/kg	18[a]	4 (22)	Not reported	4 (22) patients had 20–30% tumor regression
Welch 2006 [35]	Epithelial ovarian cancer	Sorafenib 400 mg bid + gemcitabine	26[a]	6[b] (23)	10 (38)	Median TTP 7.6 months
Amaravadi 2006 [30]	Advanced melanoma	Sorafenib 400 mg bid + temozolomide	58	10 (17)	25 (43)	4 (5) MR
Ryan 2006 [32]	Advanced RCC	Sorafenib 400 mg bid + IFN-α2b 10 MIU	58[a]	17[c] (28)	23 (38)	1 (2) CR; median PFS 6.5 months
Gollob 2006 [31]	Metastatic RCC	Sorafenib 400 mg bid + IFN-α2b 10 MIU	39[a]	10 (26)	14 (36)	1 (3) CR

bid Twice daily, *CR* complete response, *CRC* colorectal cancer, *DTIC* dacarbazine, *HCC* hepatocellular carcinoma, *IFN* interferon, *NSCLC* non-small-cell lung cancer, *MIU* million international units, *MR* minor response, *PFS* progression-free survival, *RCC* renal cell cancer, *SD* stable disease, *TTP* time to progression

[a] Not all patients were evaluable for response

[b] One patient confirmed by RECIST, five confirmed by Cancer Antigen-125 (CA-125) criteria

[c] Seven patients unconfirmed

Raf-1 activation has also been associated with potent inhibition of apoptosis, leading to cell survival [43]. Downregulating B-Raf expression using small interfering RNAs inhibits MEK/ERK activation and cell growth, and induces apoptosis in melanoma cell lines [44].

Anti-tumor activity with sorafenib combinations was equivalent to or potentially better than with either drug alone. Anti-tumor activity with sorafenib plus DTIC or paclitaxel/carboplatin was encouraging in advanced melanoma, with disease control rates of up to 78 and 84%, respectively [15, 19, 26]. These data compare favorably with DTIC or paclitaxel/carboplatin alone, in which partial responses were obtained in 10 [45] and 20% [46] of advanced melanoma patients, respectively. A Phase II trial of carboplatin/paclitaxel in melanoma patients demonstrated a low overall response rate of <10% [47]. Therefore, it is possible that the improved anti-tumor activity reported with sorafenib plus carboplatin/paclitaxel results from a synergistic interaction between these agents. In NSCLC patients, a stable disease rate of 63% was reported when treated with sorafenib combined with the targeted agent gefitinib [21]. Furthermore, sorafenib plus the targeted agent bevacizumab produced disease stabilization in 42–75% of patients with a variety of solid tumors [23, 24].

Some patients who were refractory to single-agent chemotherapy demonstrated improved tumor response when the same chemotherapy was administered in combination with sorafenib [16, 18]. For example, a high proportion of CRC patients who received sorafenib plus oxaliplatin in an extension study had stable disease, despite these patients showing previous resistance to oxaliplatin monotherapy [16]. Two heavily pretreated ovarian cancer patients, refractory to taxanes, platinum-containing chemotherapies, and anthracyclines, achieved partial responses with sorafenib plus gemcitabine [18]. Furthermore, a patient with recurrent nasopharyngeal carcinoma in the dose-escalation cohort, who was previously minimally responsive to gemcitabine treatment, had stable disease for >1 year when receiving gemcitabine plus sorafenib [18]. These findings could be attributable to sorafenib sensitizing previously treatment-refractory patients to the coadministered agents.

In addition to sorafenib's pro-apoptotic effect, its anti-angiogenic properties may render tumors more susceptible to chemotherapy by altering the vasculature. Inhibiting tumor angiogenesis can enhance delivery of cytotoxic agents by affecting the vasculature, and thereby increase the effectiveness of concomitant chemotherapy [48]. Tumor blood vessels formed under the influence of VEGF are disorganized and leaky, with high interstitial pressure, which reduces access to chemotherapies [49]. Inhibiting VEGF can reduce vessel abnormality and increase the permeability of the tumor to chemotherapies [48]. Therefore, the combination of bevacizumab plus sorafenib is an attractive therapeutic strategy because of their potentially synergistic effects on the vasculature and tumor.

Overall, sorafenib has a promising safety profile and demonstrates encouraging anti-tumor effects in combination with other anti-cancer agents in patients with several solid tumor types. In general, sorafenib at the full-recommended dose of 400 mg bid does not increase the risk of clinical toxicity of combination therapy above that expected for either agent alone. Results from these studies suggest that sorafenib in combination with other cytotoxics or targeted agents are potentially valuable new treatment alternatives for patients with advanced solid tumors.

Future directions

Given the complexity of the interactions between tumor cells and their environment, and the variety of pro-angiogenic and/or growth-promoting (autocrine) factors that tumors can produce, there is a strong rationale to combine agents with different mechanisms of action. The results from the trials reported here have led to the initiation of other combination clinical trials to evaluate sorafenib in a variety of solid tumor types. Sorafenib in combination with the chemotherapy gemcitabine or EGFR tyrosine kinase inhibitor, erlotinib, is being evaluated as first-line treatment in an ongoing Phase II trial in elderly patients or patients with a performance status of 2 affected by advanced NSCLC [50]. A Phase II trial with sorafenib combined with the anti-VEGF monoclonal antibody bevacizumab is also underway. Phase III trials have recently been initiated with sorafenib plus carboplatin/paclitaxel in advanced melanoma and NSCLC patients. The promising combination data now available for several targeted agents, and their late stage of clinical development, also raises questions about how best to optimize their use in the clinic. Optimal dosages and treatment schedules (i.e. concomitant or sequential administration of combination therapies) need to be investigated. Whether these combinations offer a PFS or overall survival benefit must still be determined. Finally, the development of appropriate biomarkers to facilitate patient selection and to monitor response to combinations of targeted therapies is also an important area for further translational research.

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