

Selected Combination Therapy with Sorafenib: A Review of Clinical Data and Perspectives in Advanced Solid Tumors

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ABSTRACT

The development of targeted therapies has provided new options for the management of patients with advanced solid tumors. There has been particular interest in agents that target the mitogen-activated protein kinase pathway, which controls tumor growth and survival and promotes angiogenesis. Sorafenib is an oral multikinase inhibitor that has been proven effective as a single-agent therapy in renal cell carcinoma, and there is a strong rationale for investigating its use in combination with other agents. In particular, targeting multiple Raf isoforms with sorafenib may help to overcome resistance to other agents, while the ability of sorafenib to induce apoptosis may increase the cytotoxicity of chemotherapeutic agents. Based on positive results in pre-clinical studies, further investigation in phase I and II

studies has shown potential antitumor activity when sorafenib is combined with cytotoxic agents in different solid tumors, including hepatocellular carcinoma and melanoma. Promising results have been reported in phase I and II studies of sorafenib combined with paclitaxel and carboplatin, with oxaliplatin in gastric and colorectal cancer, with docetaxel in breast cancer, with gemcitabine in ovarian cancer, and with capecitabine in different solid tumors. Phase II and III studies are currently investigating the use of sorafenib in combination with different agents in a variety of solid tumors. The primary objective of this review is to summarize the early clinical studies of sorafenib with cytotoxic agents and discuss future perspectives of these combinations in different tumor types. *The Oncologist* 2008;13:845–858

INTRODUCTION

Despite significant advances in our understanding and management of neoplastic diseases in recent decades, cancer remains the leading cause of death in the industrialized world, primarily as a result of the lack of effective treatments for patients with disseminated disease [1]. Although there have been significant advances in the management of primary

malignancies, solid tumors are frequently metastatic at presentation and often fail to respond to standard chemotherapies, resulting in a poor prognosis. For example, in the U.S. it has been estimated that distant metastases are present at diagnosis in 38% of colorectal cancers, 30% of esophageal cancers, 37% of lung and bronchial cancers, and 26% of pancreatic cancers [2]. Five-year survival rates for patients

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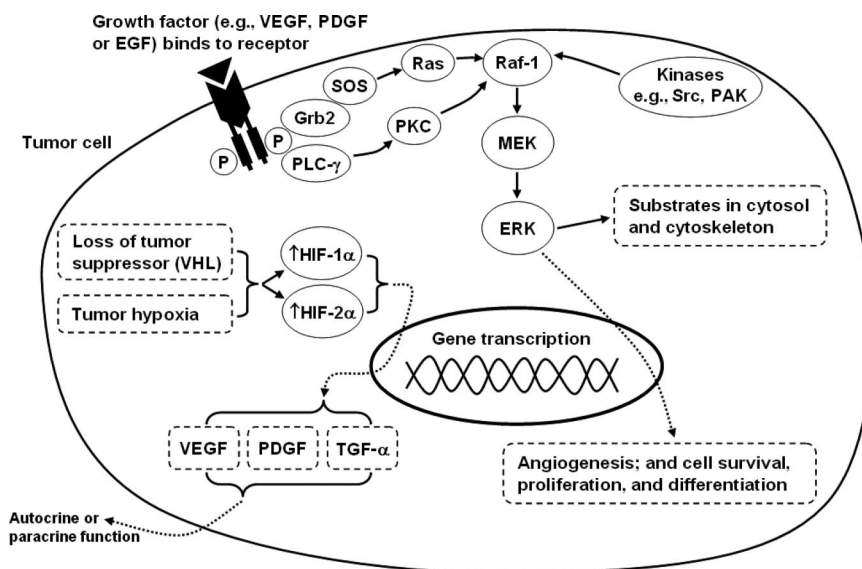


Figure 1. The organization and function of the Ras/MEK/ERK pathway. The binding of growth factors induces receptor dimerization and autophosphorylation (P) on tyrosine residues. This exchange elicits a conformational change in Ras, enabling it to bind to Raf-1 and recruit it from the cytosol to the cell membrane, where Raf-1 activation takes place. Activated Raf-1 phosphorylates and activates MEK, which in turn phosphorylates and activates ERK. Activated ERK has many substrates in the cytosol (e.g., cytoskeletal proteins, phospholipase A2, and signaling proteins, including tyrosine kinase receptors, estrogen receptors, SOS, STAT proteins, and others [108, 109]). ERK can enter the nucleus to control gene expression by phosphorylating transcription factors, leading to overproduction of components involved in angiogenesis and tumor progression. Renal cell carcinoma, in particular, is associated with the loss of the *VHL* tumor-suppressor gene and upregulation of the HIF-1 α and HIF-2 α transcription factors, leading to overexpression of growth factors (e.g., VEGF, PDGF, and TGF- α) involved in autocrine and paracrine stimulation of tumor and endothelial cells [110]. Adapted from (i) Kolch W, Kotwaliwale A, Vass K et al. The role of Raf kinases in malignant transformation. *Expert Rev Mol Med* 2002;4:1–18, with permission of Cambridge University Press; and (ii) Gollob JA, Wilhelm S, Carter C et al. Role of Raf kinase in cancer: Therapeutic potential of targeting the Raf/MEK/ERK signal transduction pathway. *Semin Oncol* 2006;33:392–406, Copyright Elsevier 2006.

Abbreviations: ERK, extracellular signal-related kinase; HIF, hypoxia inducible factor; MEK, mitogen-activated protein kinase/extracellular signal-related kinase kinase; PDGF, platelet-derived growth factor; PLC, phospholipase C; PKC, protein kinase C; SOS, son of sevenless; STAT, signal transducer and activator of transcription; TGF- α , transforming growth factor α ; VEGF, vascular endothelial growth factor; VHL, von Hippel–Lindau.

with these metastatic solid tumors are in the range of 2%–10% [2]. Therefore, there is an urgent need for new agents capable of improving outcomes in patients with metastatic solid tumors.

The advent of well-tolerated targeted agents that inhibit pivotal molecules involved in the regulation of signal transduction pathways central to tumorigenesis and progression has provided new options for the combination treatment of patients with advanced solid tumors. There has been particular interest in the ubiquitous mitogen-activated protein kinase (MAPK) pathway or Raf/MEK/ERK pathway, which controls the growth and survival of human tumors (Fig. 1), and in proangiogenic pathways, which also involve signaling through MAPK. Solid tumors frequently exhibit activating oncogenic mutations in *ras* and/or overactivation of Raf-1 kinase, resulting in dysregulated signaling through the MAPK pathway, and consequent tumor cell proliferation and angiogenesis [3]. The discovery of oncogenic *b-raf* mutations in human tumors [4] suggested that Raf kinase

isoforms, which are downstream of Ras in the highly evolutionarily conserved MAPK signal transduction pathway, are important targets for cancer therapy. Recent evidence suggests that Raf-1 is a critical regulator of endothelial cell survival during angiogenesis [5]. Inhibition of Raf-1 has also been shown to increase the efficacy of chemotherapy and radiotherapy by overcoming tumor resistance mechanisms and increasing tumor apoptosis [6].

SORAFENIB

Sorafenib (Nexavar®; Bayer Pharmaceuticals Corporation, West Haven, CT) is an oral multikinase inhibitor that inhibits tumor growth by acting on the tumor cells and cells of the tumor vasculature (i.e., vascular endothelial cells and pericytes) in preclinical tumor models. It inhibits tumor cell proliferation by targeting the MAPK pathway at the level of Raf kinase and/or induces tumor cell apoptosis [3, 7–9]. Sorafenib also potently inhibits vascular endothelial growth factor receptor VEGFR-1, VEGFR-2, VEGFR-3, and

platelet-derived growth factor receptor (PDGFR)- β tyrosine kinase autophosphorylation [3, 10]. These proangiogenic receptor tyrosine kinases (RTKs) signal through Raf/MEK/ERK to induce proliferation and prolong the survival of vascular endothelial cells, which form new blood vessels. By signaling through Raf, these proangiogenic RTKs also promote the proliferation, increase the survival, and elicit the recruitment of pericytes, which stabilize the newly formed blood vessels [11]. Data from preclinical studies demonstrated that sorafenib inhibited in vivo tumor growth in a dose-dependent manner [3] and that it had cytostatic activity in preclinical models of human cancer, including pancreatic, ovarian, breast, melanoma, lung, and colon xenografts harboring oncogenic *k-ras* or *b-raf* mutations [12]. In some tumor models, sorafenib's growth inhibitory effects were associated with an antiproliferative effect mediated via inhibited signaling through the MAPK pathway (i.e., reduced ERK-1/ERK-2 phosphorylation) [3]. Sorafenib was also associated with an antiangiogenic effect, in addition to inhibition of signaling through MAPK, in several xenograft models (e.g., MDA-MB-231 breast, HT-29 colon, and UACC 903 and Lu205 melanoma) [3, 13]. In another xenograft model (Colo-205 colon) and in a murine model of renal cancer (Renca), sorafenib acted by an antiangiogenic mechanism without evidence of an antiproliferative effect [3, 14]. However, although the growth of non-small cell lung cancer (NSCLC) cell lines harboring oncogenic *k-ras* mutations was inhibited by sorafenib, this effect was not associated with MAPK inhibition [3]. Sorafenib induced apoptosis by downregulating the antiapoptotic protein Mcl-1 in these NSCLC lines [15]. Sorafenib has also been shown to induce apoptosis in a wide variety of human tumor cell lines [7–9, 15, 16].

Clinical trials evaluating sorafenib as a single agent in patients with advanced solid tumors have also yielded encouraging results, especially in renal cell carcinoma (RCC), based on which sorafenib was approved in the U.S. in December 2005. In a phase II trial with a randomized discontinuation design, which involved 502 patients with multiple tumor types, 202 RCC patients were evaluated. In that trial, significantly more patients treated with sorafenib (16 of 32, 50%) were progression free at 12 weeks postrandomization, compared with those on placebo (6 of 33, 18%; $p < .0077$) [17, 18]. Confirmation of the clinical efficacy of sorafenib in patients with advanced RCC was provided by the subsequent phase III Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGETs). In TARGETs, which was the largest study conducted to date in RCC ($n = 903$ in the intention-to-treat cohort), patients who had received one prior systemic therapy received continuous oral sorafenib or placebo [19]. Sorafenib was associated with a

significant twofold longer median progression-free survival (PFS) duration compared with placebo treatment (24 weeks versus 12 weeks; $p < .000001$). Furthermore, this clinical benefit was independent of gender, age, prior therapy, Memorial Sloan-Kettering Cancer Center risk group, baseline Eastern Cooperative Oncology Group performance status, and time since diagnosis. Patients receiving sorafenib in TARGETs experienced an estimated 39% longer overall survival (OS) time relative to those on placebo ($p < .018$; hazard ratio, 0.72), according to a planned interim analysis [19]. In addition to promising preclinical and clinical findings culminating in the approval of sorafenib for the treatment of advanced RCC, its mechanism of action and good safety and tolerability suggest that it would be a useful combination treatment option for advanced cancer. This review discusses the preclinical and clinical data resulting from studies that use sorafenib in combination with other anticancer agents in a wide variety of solid tumors, and provides a guide to the most promising developments.

RATIONALE FOR COMBINATION THERAPY WITH SORAFENIB

Sorafenib has several important properties that suggest it would be useful as a combination treatment option for patients with advanced cancer. Sorafenib's multiple targets, including Raf-1 [20, 21], wild-type B-Raf, oncogenic *b-raf* V600E, and proangiogenic RTKs [3], enable it to act on the tumor and tumor vasculature to induce apoptosis and inhibit proliferation and angiogenesis in preclinical models, possibly through the downregulation of Mcl-1 [8, 9, 15], and provide sorafenib with the potential for activity against a wide variety of tumor types. For example, oncogenic *ras* mutations, which hyperactivate Raf kinase isoforms, occur in approximately 90% of pancreatic cancers, 50% of thyroid cancers, 50% of colon cancers, and 30% of lung cancers [22]. Oncogenic *b-raf* mutations occur in approximately 15% of all cancers, with a particularly high incidence in melanoma (66%) [4]. In addition, inhibition of VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR- β may provide a means to target a variety of well-vascularized solid tumors that are difficult to treat and associated with a poor prognosis, such as hepatocellular carcinoma (HCC), melanoma, NSCLC, and gastric cancer. Sorafenib's activity in RCC may be mediated via inhibition of VEGFRs [23].

The targeting of multiple Raf isoforms and RTKs by sorafenib may also provide a means to overcome multidrug resistance genes (*MDR* is upregulated by Raf-1). For example, imatinib targets a PDGFR- α oncogene involved in chronic eosinophilic leukemia, but may be compromised by the development of resistance mutations. Sorafenib has

been shown to be a potent inhibitor of an imatinib-resistant chronic eosinophilic leukemia (T674I mutation), inducing apoptosis at nanomolar concentrations [24]. Sorafenib has also been shown to have activity against thyroid carcinoma cells, including mutants resistant to anilinoquinazolines and pyrazolopyrimidines [25].

Sorafenib's ability to induce apoptosis, possibly by inhibiting the MEK/ERK-independent effects of Raf-1, in a wide variety of human tumor cell lines, could complement the cytotoxic effects of standard chemotherapies. There is evidence to suggest that inhibition of Raf-1 can resensitize tumor cells resistant to radio- or chemotherapy [6, 26].

PRECLINICAL STUDIES

The administration of sorafenib in combination with other agents has been examined in several preclinical models. In xenograft models, concomitant sorafenib did not impair the efficacy or increase the toxicity of the standard chemotherapy agents gemcitabine, vinorelbine, and irinotecan [27]. In these preclinical studies, irinotecan and sorafenib delayed tumor growth in the DLD-1 colon tumor model by 71% and 100%, respectively, whereas combining the two agents resulted in a 229% synergistic delay. Moreover, vinorelbine and sorafenib delayed growth in the NCI-H460 NSCLC model by 32% and 104%, respectively, compared with 133% when both agents were given in combination. Gemcitabine and sorafenib resulted in growth delays of 154% and 112% in MiaPaCa-2 pancreatic tumor xenografts, compared with a 221% growth delay when used in combination. In addition, there were additive or moderate synergistic effects when sorafenib was administered in combination with cytotoxic agents, such as paclitaxel, 5-fluorouracil, and SN-38 (the most active metabolite of CPT-11), in human colon carcinoma cells [28]. However, sorafenib has been shown to reduce the activity of oxaliplatin and cisplatin in colorectal cancer cell lines [29].

CLINICAL STUDIES

On the basis of promising preclinical evaluations, several clinical trials were initiated evaluating sorafenib in combination with a variety of anticancer agents in several different tumor types (Table 1).

Renal Cell Carcinoma (RCC)

RCC is characterized by the frequent loss of the von Hippel-Lindau tumor suppressor gene, which results in the loss of one of the critical mechanisms for regulating the level of hypoxia-inducible factors 1 and 2, leading to overproduction of growth factors (e.g., VEGF, PDGF, and transforming growth factor α) by tumor cells and tumor growth via possible autocrine or paracrine loops (Fig. 1) [30, 31]. Ther-

apeutic strategies to inhibit the function of these important pathways have been effective in preventing tumor angiogenesis in preclinical models of renal cancer [32].

Single-agent therapy with sorafenib has been shown to have activity in RCC, probably as a consequence of inhibition of VEGFRs [33]. The benefits of sorafenib as a single agent in RCC provide a strong rationale for evaluating its combination with other antiangiogenic therapies also known to be active in this tumor type, such as sunitinib and bevacizumab. The combination of sorafenib and bevacizumab is under investigation in a clinical trial of advanced RCC [34]. In addition, the combination of sorafenib and interferon has been investigated in phase II studies of patients with locally advanced or metastatic kidney cancer. Preliminary data showed that sorafenib combined with low-dose interferon in a phase II randomized study did not provide superior clinical benefit compared with sorafenib alone in patients with metastatic RCC [35]. However, an uncontrolled phase II study investigating higher doses of interferon (9 MU three times a week or 3 MU five times a week) in combination with sorafenib showed promising efficacy in which 16 of 63 patients (25%) achieved a partial response (PR) and 26 of 63 (41%) had stable disease (SD) [36]. At present, this trial represents possibly the most promising evidence of antitumor activity from a sorafenib-based combination approach in metastatic RCC [35, 36], and warrants further investigation in randomized controlled studies, particularly in patients with clear-cell histology.

A phase I/II trial is ongoing to study the combination of sorafenib, gemcitabine, and capecitabine in patients with unresectable or metastatic RCC [37]. Sorafenib is also being studied in phase I/II studies involving patients with metastatic RCC in combination with perifosine, an oral alkylphosphocholine with effects on the MAPK and Janus kinase pathways [38]. Preliminary results from the phase II trial showed that three of nine patients (33%) with metastatic RCC evaluable for response achieved a PR (lasting 4–9 months) and another three patients had SD (lasting 9–10 months) [38].

Melanoma

Oncogenic *b-raf* mutations occur in up to 70% of melanomas, and the MAPK pathway is often hyperactivated in this tumor type [4]. ERK is constitutively activated in melanoma cells expressing oncogenic *b-raf*, and this activity is required for proliferation. Sorafenib targets *b-raf* signaling in vivo and has been shown to induce a substantial growth delay in human melanoma tumor xenografts [39]. There is also evidence that there is elevated expression of several angiogenic factors, including VEGF, basic fibroblast growth factor, and interleukin-8, in primary cutaneous melanomas

Table 1. A summary of studies of sorafenib in combination with other drugs

Study	Patients	Treatments	Toxicities (dose limiting or grade 3 or 4)	RPTD	Comments
Jonasch et al. [35]	60 patients enrolled (55 evaluable) with untreated conventional (clear-cell) metastatic RCC	Sorafenib, 400 mg po bid with or without IFN- α , 0.5 MU s.c. bid	—	—	Median TTP same in both arms (9.3 mos); low-dose IFN + sorafenib did not improve response over sorafenib alone
Bracarda et al. [36]	63 patients with metastatic RCC that had a clear-cell component of 50%	Oral sorafenib, 400 mg bid continuously; s.c. IFN, 9 MU three times a wk (arm A) or 3 MU five times a wk (arm B) initiated 7 days after sorafenib	Only data from arm A: fatigue, 19%; skin rash, 8%; hypophosphatemia, 43%; hand-foot syndrome, 22%; anorexia, stomatitis, hyperamylasemia, 11% each; diarrhea, 8%; hyperlipasemia, 5%	—	PR in 16 patients; SD in 26 patients
Stephenson et al. [38]	241 patients (13 with RCC, 9 evaluable for response)	Perifosine escalated from 50 mg qd to 50 mg tid; sorafenib escalated from 400 mg qd to 400 mg bid for 4/6 wks	No grade 3 or 4 toxicities and increase in hand-foot syndrome	—	PR in 3 patients (33%), duration 4, 6.5, and 9 mos, respectively; SD in 3 patients (33%), duration 9+, 9+, and 10 mos, respectively; study ongoing
Flaherty et al. [42]	35 patients with melanoma	Carboplatin, AUC 6; paclitaxel, 225 mg/m ² q3w (maximum 6 cycles); sorafenib, days 2–19 at doses of 100 mg bid, 200 mg bid, or 400 mg bid	Neutropenia, grade 3 in 20% and grade 4 in 43%; thrombocytopenia, grade 3 in 43% and grade 4 in 3%; hypertension, grade 3 in 1 patient; thrombosis, 3 patients; HFSR, grade 3 in 4 patients; vomiting, grade 3 in 3 patients; infection, 6 patients; neuropathy grade 3, 1 patient; hypersensitivity, 3 patients	—	PR in 14 patients; SD in 15 patients; no evidence of additive toxicities or PK interactions; antitumor activity independent of B-Raf status
Agarwala et al. [43]	270 patients with advanced melanoma	Paclitaxel, 225 mg/m ² , and carboplatin, AUC 6 i.v. on day 1, q3w (P/C) + oral placebo ($n = 135$) or oral sorafenib, 400 mg po bid on days 2–19 q3w ($n = 135$); mandatory dose reduction after cycle 4 to paclitaxel, 175 mg/m ² , and carboplatin, AUC 5	P/C + placebo vs P/C + sorafenib: neutropenia, 45% vs 49%; febrile neutropenia, 7% vs 9%; thrombocytopenia, 12% vs 28%; sensory neuropathy, 13% vs 20%; thrombosis/embolism, 6% vs 4%; rash/desquamation, 0% vs 7%; HFSR, 0% vs 7%; fatigue, 10% vs 16%; diarrhea, 3% vs 8%; hemorrhage, 3% vs 2%; there were 2 deaths, possibly related to treatment with P/C + sorafenib	—	Median PFS of 17.9 wks vs 17.4 wks for P/C + placebo vs P/C + sorafenib; addition of sorafenib to P/C did not improve PFS or ORR in this second-line patient population
Eisen et al. [46]	83 patients with advanced melanoma treated (74 evaluable for response)	Oral sorafenib, 400 mg bid daily, combined with repeated 21-day cycles of i.v. DTIC, 1,000 mg/m ² given on day 1 of each cycle	Grade 3 or 4 drug-related adverse events included: neutrophils, 33%; platelets, 22%; HFSR, 8%; fatigue, 7%; abdominal pain, 6%; only 1 patient had febrile neutropenia	—	PR in 8 (10%) patients; SD in 34 (41%) patients; median PFS was 14 wks; median OS was 41 wks
McDermott et al. [48]	101 patients with advanced melanoma	DTIC, 1,000 mg/m ² q21d, + oral placebo ($n = 50$) or sorafenib, 400 mg bid ($n = 51$)	DTIC + placebo vs DTIC + sorafenib: neutropenia, 12% vs 33%; leukopenia, 6% vs 14%; thrombocytopenia, 18% vs 35%; thrombosis/embolism, 0% vs 6%; hypertension, 0% vs 8%; HFSR, 0% vs 4%; CNS hemorrhage, 0% vs 8%	—	For DTIC + placebo vs DTIC + sorafenib, median PFS of 11.7 wks vs 21.1 wks; PFS rate at day 180, 18% vs 41%; ORR, 12% vs 24%
Azad et al. [49]	38 patients with advanced solid tumors	Sorafenib, 200 mg po bid, + bevacizumab, 5 mg/kg i.v. q2w (dose level 1); each drug escalated sequentially ($n = 14$) Sorafenib, 200 mg po bid (arm 1) ($n = 12$) or bevacizumab, 5 mg/kg i.v. q2w ($n = 12$) (arm 2) for 1 mo, then sorafenib + bevacizumab thereafter	Hypertension, 10; proteinuria, 2, DLTs; thrombocytopenia, 1, DLT	Sorafenib, 200 mg po bid, + bevacizumab, 5 mg/kg i.v. q2w (dose level 1)	PR in 6 of 14 patients with ovarian cancer
Soria et al. [50]	23 patients with advanced solid tumors	DTIC, 1,000 mg/m ² , 21-day cycle, 1-hour infusion; sorafenib, 400 mg bid, was given on days 2–21 in cycle 1 and continuously thereafter	HFSR, 4%; fatigue, 26%; thrombocytopenia, 22%; neutropenia, 13%	DTIC, 1,000 mg/m ² + sorafenib, 400 mg bid	1 confirmed PR (melanoma); 13 SD (median duration, 161 days)
Amaravadi et al. [51]	167 patients with advanced melanoma accrued (147 evaluable)	Sorafenib, 400 mg po bid continuously; after 1 wk of sorafenib alone, patients without brain metastases or prior TMZ (arms A + B) received either ED: TMZ, 75 mg/m ² po qd for 6/8 wks (arm A, $n = 38$) or STD: TMZ, 150 mg/m ² po qd for days 1–5 of 28 (arm B, $n = 38$); patients with prior TMZ received ED (arm C, $n = 38$); patients with brain metastases without prior TMZ received STD (arm D, $n = 53$)	Hand-foot syndrome, 14%; rash, 9%; nausea, 9%; diarrhea, 5%; grade 3 lymphopenia was more common in arm A than in arm B (43% vs 16%)	—	Arm A + B, PR 19%; SD 48%; arm C, SD 27%; arm D, PR 17%, SD 49%; <i>BRAF</i> mutational status not predictive of response or PFS; sorafenib + TMZ is active in patients with brain metastases

(continued)

Table 1. (Continued)

Study	Patients	Treatments	Toxicities (dose limiting or grade 3 or 4)	RPTD	Comments
Brendel et al. [105]	23 patients with advanced melanoma and other solid tumors	DTIC, 1,000 mg/m ² given q3w starting on day 1 of cycle 1; sorafenib, 400 mg bid given on days 2–21 in cycle 1 and continuously thereafter	—	DTIC, 1,000 mg/m ² + sorafenib, 400 mg bid	PK analysis suggests sorafenib + DTIC lowers DTIC exposure; increase in metabolite AIC may correlate with toxicity
Richly et al. [55]	34 patients with advanced solid tumors	Doxorubicin, 60 mg/m ² q3w (maximum 6 cycles); sorafenib on days 4–21 in first cycle then continuous at doses of 100 mg (cohort 1, <i>n</i> = 6), 200 mg (cohort 2, <i>n</i> = 6), or 400 mg (cohort 3–4, <i>n</i> = 22) bid	Neutropenia, grade 3 or 4 in 1 patient (cohort 1); fatigue, grade 3 in 4 patients (<i>n</i> = 3 cohort 1, <i>n</i> = 1 cohort 2); HFSR, 4 patients (cohort 3)	Sorafenib, 400 mg bid; doxorubicin, 60 mg/m ²	SD in 15 patients; PR in 1 patient (mesothelioma); encouraging results in HCC (SD in all 4 patients); cohort 3–4, different tablets used
Richly et al. [57]	18 patients (13 evaluable for tumor response) with solid tumors (HCC, <i>n</i> = 17; cholangiocellular cancer, <i>n</i> = 1)	Doxorubicin, 60 mg/m ² q3w (1–6 cycles); sorafenib, 400 mg on days 4–21 in first cycle then continuous	Neutropenia, 11 patients; diarrhea, grade 3 in 2 patients; HFSR, grade 3 in 1 patient; grades 3 and 4 asymptomatic hypomagnesemia in 13 patients (grade 3 in 11 patients and grade 4 in 2 patients)	—	Sorafenib slightly increased C _{max} and AUC of doxorubicin and doxorubicinol; doxorubicin had no impact on PK of sorafenib
Siu et al. [63]	42 patients with solid tumors (including 23 in extended pancreatic cancer cohort)	Gemcitabine, 1,000 mg/m ² weekly × 7, 1-wk rest then weekly × 3 q4w; sorafenib dose-escalation phase, 100 to 200 mg bid, or fixed-dose cohort, 400 mg bid	Dose-escalation cohort: platelets, 31%; neutrophils, 21%; lymphocytes, 37%; hypertension, 16%; fatigue, 21%; HFSR, 5%; ALT, 5%; lipase, 37%; headache, 16%; fixed-dose cohort: platelets 26%, neutrophils 13%, lymphocytes 9%, hypertension 0%, fatigue 9%, HFSR 4%, ALT 13%, lipase 4%, headache 0%	Sorafenib, 400 mg bid; gemcitabine, 1,000 mg/m ²	PR in 2 patients (each with ovarian cancer); SD in 25 patients (13 pancreatic cancer); no PK interactions; combination of potential interest, mainly in ovarian cancer
Wallace et al. [64]	17 patients with advanced pancreatic cancer	Sorafenib, 400 mg orally bid days 1–28; gemcitabine, 1,000 mg/m ² over 30 minutes days 1, 8, and 15 q28d	Neutropenia, 29%; thrombocytopenia, 6%; neutropenic fever, 0%; thrombosis, 18%; fatigue, 18%; rash, 12%; dehydration, 12%; nausea, 12%; hand–foot syndrome, 12%; hypertension, 6%; diarrhea, 6%; gastrointestinal bleeding, 6%	—	No objective responses; SD in 3 patients (23%); median PFS, 3.2 mos; study did not meet response criteria to proceed to a second stage of accrual
Welch et al. [68]	43 patients with recurrent ovarian cancer accrued (38 evaluable)	Gemcitabine, 1,000 mg/m ² i.v. weekly for 7 of 8 wks in first cycle, then weekly for first 3 wks of each subsequent 4-wk cycle; oral sorafenib, 400 mg bid given continuously	The most frequent grade 3 or 4 adverse events were: lymphopenia, 32%; neutropenia, 21%; thrombocytopenia, 21%; hand–foot syndrome, 21%; fatigue, 16%; hypokalemia, 16%	—	PR in 2 patients (4.7%); SD in 26 patients (60.4%); 9 of 26 patients (36.6%) with abnormal baseline CA-125 level achieved a CA-125 response; median TTP, 5.4 mos; median OS, 13.3 mos
Kupsch et al. [73]	37 patients with solid tumors (CRC, 49%; Mel, 14%; RCC, 8%)	Oxaliplatin, 130 mg/m ² q3w; sorafenib, 200 mg (cohort 1) or 400 mg (cohorts 2A, 2B, and 3) bid	Thrombocytopenia, 1 patient in cohort 3; leukopenia, 1 patient in cohort 2A; diarrhea, 1 patient in cohort 2B, 1 patient in cohort 3	Sorafenib, 400 mg bid; oxaliplatin, 130 mg/m ²	No PK interactions; PR in 2 patients with gastric cancer; SD in 5 of 8 patients in cohort 2A, 5 of 10 in cohort 2B, and 7 of 9 in cohort 3; of potential interest in CRC and ovarian cancer
Awada et al. [77]	27 patients with advanced solid tumors	Docetaxel, 75 or 100 mg/m ² 1-hr i.v., day 1 + sorafenib, 200 or 400 mg bid, days 2–19 of each 21-day (3-wk) cycle with a 3-day break in dosing around the administration of docetaxel; cohort 1 (<i>n</i> = 6), 200 mg bid, 75 mg/m ² ; cohort 2 (<i>n</i> = 6), 200 mg bid, 100 mg/m ² ; cohort 3 (<i>n</i> = 5), 400 mg bid, 100 mg/m ² ; Cohort 4 (<i>n</i> = 10), 400 mg bid, 75 mg/m ²	DLTs mainly: dermatologic, 41%; gastrointestinal, 26%; constitutional symptoms, 22%	Docetaxel, 75 or 100 mg/m ² + sorafenib, 400 mg bid	PR in 3 (11%) patients (breast, lung, and esophageal cancers); SD in 14 (52%) patients; median TTP, 127–179 days; concomitant docetaxel + sorafenib resulted in mean increase in docetaxel AUC _{0–24} of 5%–80%; frequency of dermatologic toxicities was higher than expected for single agents
Hong et al. [79]	40 patients with advanced solid tumors (19 evaluable for response)	Sorafenib, 400 mg qd; tipifarnib, 100 mg po qd (cohort 0); sorafenib, 400 mg qd; tipifarnib, 100 mg po qd (cohort 1); sorafenib, 400 mg qd; tipifarnib, 100 mg po bid (cohort 2); sorafenib, 400 mg po qam, 200 mg po qpm; tipifarnib, 100 mg po bid (cohort 3); sorafenib, 400 mg po qam, 200 mg po qpm; tipifarnib, 200 mg po bid (cohort 4); sorafenib, 400 mg po qam, 200 mg po qpm; tipifarnib, 300 mg po bid (cohort 5); sorafenib, 400 mg po bid; tipifarnib, 100 mg po bid (cohort 6)	DLT, rash (<i>n</i> = 5; 12.5%); grade 3 toxicities: lymphopenia, 52%; rash, 48%	Sorafenib, 400 mg qam, 200 mg qpm; tipifarnib, 100 mg bid	22 patients SD (8–44 wks); PR in 3 patients with medullary thyroid cancer and 2 patients with papillary thyroid cancer; no PK interaction between sorafenib and tipifarnib; toxicity significantly greater in combination

(continued)

Table 1. (Continued)

Study	Patients	Treatments	Toxicities (dose limiting or grade 3 or 4)	RPTD	Comments
Awada et al. [106]	35 patients with advanced solid tumors	Sorafenib, bid days 8–21 of cycle 1, and continuously thereafter; capecitabine bid from day 1 in a 2 wks on/1 wk off schedule; cohort 1: sorafenib, 200 mg bid with capecitabine, 2,100 mg/m ² per day; cohort 2: sorafenib, 400 mg bid with capecitabine, 2,100 mg/m ² per day; cohort 3: sorafenib, 200 mg bid for the first 2 cycles then 400 mg bid thereafter with capecitabine, 2,100 mg/m ² per day; cohort 4: sorafenib, 400 mg bid with capecitabine, 1,700 mg/m ² per day	DLTs in 6 patients, 2 in cohort 1, 1 in each of cohorts 2 and 3, and 2 in cohort 4; HFSR, 6 patients; diarrhea and mucositis, each in 1 patient who also had HFSR as a DLT	Sorafenib, 400 mg bid plus capecitabine, 1,700 mg/m ²	In cohort 1, one heavily pretreated patient with breast cancer and skin lymphangitis had tumor regression; SD ≥4 mos in 13 patients; tumor shrinkage in 2 patients in cohort 4 (RCC, <i>n</i> = 1; urothelial cancer, <i>n</i> = 1); no impact of capecitabine on sorafenib PK; concomitant sorafenib moderately increased capecitabine and 5-fluorouracil exposure
Mross et al. [107]	18 patients with solid tumors	CPT-11, 125 mg/m ² i.v. on days 1, 8, 15, 22, and 43 then 2-wk rest; sorafenib, 100 mg (<i>n</i> = 6), 200 mg (<i>n</i> = 6), or 400 mg (<i>n</i> = 6) bid	Diarrhea, 2 patients; leukopenia, 1 patient	—	No significant PK interactions; of potential interest and to be studied in CRC, cervical and gastric cancer, and NSCLC and in particular in patients refractory to CPT-11

Abbreviations: AIC, 5-aminoimidazole-4-carboxamide; ALT, alanine aminotransferase; AUC, area under the curve; bid, twice daily; CA-125, cancer antigen 125; C_{max}, maximum concentration; CNS, central nervous system; CRC, colorectal cancer; DLT, dose-limiting toxicity; DTIC, dacarbazine; ED, extended dosing; HCC, hepatocellular carcinoma; HFSR, hand-foot skin reaction; IFN, interferon; Mel, melanoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; po, orally; PR, partial response; q3w, every 3 weeks; qam, every morning; qd, once daily; qpm, every afternoon; RCC, renal cell carcinoma; RPTD, recommended phase II dose; SD, stable disease; STD, standard dosing; tid, three times daily; TMZ, temozolomide; TTP, time to progression.

[40]. The overproduction of VEGF in association with VEGFR expression favors cell growth and survival of melanoma cells through the MAPK and phosphatidylinositol 3' kinase signaling pathways. These data support the involvement in melanoma growth and survival of a VEGF-dependent internal autocrine loop mechanism, at least in vitro [41]. Therefore, there is the potential for sorafenib to target melanoma through inhibition of VEGFR-1, VEGFR-2, and VEGFR-3, as well as through inhibition of Raf kinase.

The effects of the combination of paclitaxel, carboplatin, and sorafenib have been investigated in a phase I/II trial of 35 patients with progressive stage IV melanoma pretreated with no more than three previous chemotherapy regimens [42]. The preliminary results showed a high rate of PR (40%) and SD (43%), but the antitumor activity was independent of *b-raf* mutational status. Responses were observed mainly in patients with skin, subcutaneous, and lymph node metastases (stage M1a) and a limited number of previous therapies. These results are encouraging and support further evaluation of this combination in patients with melanoma. A phase III trial investigating the efficacy of paclitaxel plus carboplatin with or without sorafenib did not show any benefit in terms of PFS or objective responses as second-line treatment in patients with advanced melanoma [43]. The PFS rates at day 180 were 32% and 29% and the overall response rates were 12% and 11% for paclitaxel and carboplatin plus sorafenib versus paclitaxel and

carboplatin plus placebo, respectively [43]. An ongoing phase III trial is investigating the combination of sorafenib and repeated cycles of paclitaxel and carboplatin in patients with unresectable stage III or IV melanoma [44].

Sorafenib was also evaluated in combination with repeated cycles of dacarbazine (DTIC) in a single-center, open-label, phase I, dose-escalation trial in patients with metastatic melanoma [45]. Among 18 evaluable patients, three (17%) had PRs and 11 (61%) had SD. This combination was further evaluated in clinical trials, including a phase II open-label, first-line, uncontrolled study as well as a phase II randomized, placebo-controlled study in patients with unresectable stage III or IV melanoma. In the uncontrolled phase II study, sorafenib and DTIC were well tolerated and yielded promising efficacy results in these patients with a poor prognosis [46]. Eight patients (10%) achieved PRs and 34 (41%) had SD; the median PFS duration was 14 weeks and the median OS time was 41 weeks [46]. These data are encouraging, compared with DTIC alone, which achieved a response rate of 7.5% and a PFS time of 6 weeks [47]. Results from a placebo-controlled study support a better efficacy trend in terms of objective responses and PFS compared with DTIC alone in advanced melanoma [48]. The median PFS times were 21.1 versus 11.7 weeks for sorafenib in combination with DTIC compared with DTIC plus placebo, respectively [48].

The evidence that VEGF is upregulated in melanoma

provides a rationale for investigating the use of anti-VEGF agents, such as bevacizumab. Such agents might have the potential for use in combination therapy for melanoma to enhance the antiangiogenic effects alongside the targeting of Raf/MEK/ERK by sorafenib. Preliminary results from an ongoing phase I trial investigating the combination of bevacizumab and sorafenib in patients with refractory, metastatic, or unresectable solid tumors showed that PRs were reported in six of 14 patients (43%) with ovarian cancer as well as one of three patients (33%) with RCC [49]. The clinical benefit of sorafenib in combination with DTIC in advanced solid tumors has been supported, in part, by preliminary data from a phase I study, in which one of 22 patients (melanoma) achieved a PR and 13 of 22 (59%) had SD as their best response [50].

Sorafenib has also been evaluated in combination with temozolomide, an oral alkylating agent approved for the treatment of refractory anaplastic astrocytoma and for patients with metastatic melanoma with or without brain metastases. Results from a four-arm phase II trial demonstrated encouraging antitumor activity and tolerability of this combination in patients with metastatic melanoma. An overall response rate of 19% was observed in 78 patients across two arms of the study [51].

Overall, the most promising sorafenib-based combination approach appears to involve DTIC, which produced a fairly consistent level of preliminary responses or SD in patients with advanced melanoma [46, 48, 50].

Hepatocellular Carcinoma (HCC)

HCC is a highly vascularized tumor that expresses high levels of VEGF [52, 53]. This provides a strong rationale for investigating the antiangiogenic properties of sorafenib in this tumor type. Findings from a randomized phase III trial of sorafenib versus placebo performed in 602 treatment-naïve patients with advanced HCC were presented at the 2007 American Society of Clinical Oncology Annual Meeting, and helped to establish sorafenib as first-line treatment for patients with advanced HCC [54]. The data demonstrated a significantly longer OS time (hazard ratio, 0.69; $p = .0006$) and median time to progression (hazard ratio, 0.58; $p = .000007$) for patients in the sorafenib arm [54].

Early evidence of the potential for combining sorafenib with other agents in the treatment of HCC was provided by a phase I study of sorafenib and doxorubicin and a phase II study of single-agent sorafenib. In the phase I trial, four of 16 patients with SD following treatment with sorafenib in combination with doxorubicin had HCC [55]. In the phase II trial, sorafenib monotherapy also had antitumor activity in HCC patients [56]. These findings led to the initiation of an extended phase I trial of sorafenib and doxorubicin in 18

patients with advanced HCC. That trial showed that the safety profile of the sorafenib and doxorubicin combination was similar to that expected with either agent alone [57]. Of 13 evaluable patients, the best response observed was SD for at least 6 months in four patients (30%) and at least 3 months in seven patients (54%). The high proportion of patients included with previous systemic therapy (35%) may explain the low objective response rate in this trial. However, based on the available data and the absence of known efficacy of systemic chemotherapy in HCC [58], it is probable that doxorubicin did not add much to the activity of this combination. To resolve this issue, a randomized, controlled phase II/III study is currently evaluating the efficacy of sorafenib in combination with doxorubicin versus doxorubicin alone in patients with advanced HCC [59].

Pancreatic Cancer

Pancreatic cancer is associated with a high frequency of activating oncogenic *k-ras* mutations [60]. In addition, VEGF-A expression in pancreatic adenocarcinoma is associated with a greater likelihood of disease progression, poor prognosis, and a higher risk for metastatic spread [61, 62]. Therefore, sorafenib could have the potential for activity in pancreatic cancer through inhibition of the Raf/MEK/ERK pathway at the level of Raf kinase and through activity against VEGFRs. However, a phase I trial demonstrated modest preliminary antitumor activity with sorafenib and gemcitabine in patients with pancreatic cancer [63]. In the 23 patients with pancreatic cancer, one patient had an unconfirmed PR and 11 had SD. The combination appeared to have similar activity to that of gemcitabine alone. A phase II trial of sorafenib and gemcitabine in patients with advanced pancreatic cancer also did not demonstrate significant clinical benefit. Although the combination was generally well tolerated, only three of 13 (23%) patients evaluable for response achieved SD, and the study did not meet the response criteria to proceed to a second stage of accrual [64]. An ongoing randomized phase II trial investigating treatment of metastatic pancreatic cancer with the combination of sorafenib and gemcitabine, compared with gemcitabine alone, should clarify whether this combination has activity against this tumor type [65].

Ovarian Carcinoma

Ovarian cancer is associated with a high frequency of oncogenic *b-raf* mutations [66], and might therefore be sensitive to treatment with sorafenib. In addition, high tissue expression of VEGF-C and VEGFR-2 has been associated with a poor prognosis in ovarian carcinoma [67], and VEGF upregulation is frequent in this tumor type.

The combination of gemcitabine and sorafenib was as-

sociated with a promising outcome in a study of patients with advanced solid tumors, with two confirmed PRs among the six patients with ovarian cancer [63]. A phase II trial investigating sorafenib in combination with gemcitabine in patients with advanced ovarian tumors reported few objective responses (5% had PRs), but demonstrated an encouraging incidence of SD (26%) [68]. The median time to progression was 5.4 months and the median OS time was 13.3 months. Furthermore, 37% of patients with an abnormal baseline cancer antigen (CA)-125 level achieved a CA-125 response using Gynecologic Cancer Intergroup criteria. Clearly, based on these findings, the combination of sorafenib with gemcitabine is emerging as a promising treatment approach in patients with ovarian cancer [63, 64, 68]. An ongoing phase II randomized trial is investigating sorafenib with or without paclitaxel and carboplatin in recurrent platinum-sensitive ovarian cancer [69].

Gastric and Colorectal Cancers

VEGF is expressed in many gastric carcinoma cell lines and may play an important role in cell growth [70], providing a rationale for treatment with sorafenib. There is also a need to explore the value of combination therapies given the limitations of current therapies for advanced gastric and colorectal cancer, which are largely palliative [71]. Although several combination regimens showed remarkable response rates in phase II trials in gastric cancer, the results in well-controlled randomized trials have been far less impressive [72].

In contrast to the preclinical data [29], the combination of sorafenib and oxaliplatin did not appear to result in antagonistic pharmacologic interactions in a trial involving 27 patients with refractory solid tumors enrolled in an initial dose-escalation phase and an additional 10 patients with oxaliplatin-refractory colorectal cancer enrolled in an extension phase [73]. No pharmacokinetic interaction between sorafenib and oxaliplatin was detected in this trial, which also resulted in PRs in two patients with gastric cancer. It would be of interest to study this combination in gastric cancer, because the available regimens prescribed in this disease, although active, are usually toxic. A phase II trial is currently investigating the combination of sorafenib, docetaxel, and cisplatin in patients with unresectable metastatic or locally advanced gastric or gastroesophageal junction cancer [74].

Breast Cancer

Growth factors and hormones have been shown to be involved in the regulation of breast cancer cell proliferation, which requires activation of MAPK via Ras and Raf [75]. In addition, VEGF is overexpressed in breast cancer [76], sug-

gesting that sorafenib may be of potential benefit in the treatment of breast cancer.

A phase I combination trial of docetaxel and sorafenib has demonstrated three PRs, one in a patient with breast cancer [77]. There may also be a rationale for evaluating the use of sorafenib in combination with hormonal therapies in patients with breast cancer, especially in patients who are resistant to hormone therapy. This concept is under investigation in a study of the combination of anastrozole and sorafenib in women with metastatic breast cancer [78].

Thyroid Cancer

A phase I combination trial of sorafenib and tipifarnib, an inhibitor of farnesyltransferase that is critical for Ras activity, has demonstrated responses in medullary/papillary thyroid patients. In a study of 40 patients with advanced solid tumors, a confirmed PR was seen in three patients with medullary thyroid cancer and in two patients with papillary thyroid cancer [79]. These preliminary data suggest that targeting multiple points in the Ras/Raf/MEK pathway may be an effective way to modulate mitogenesis and tumorigenesis in thyroid cancers.

OTHER AGENTS IN DEVELOPMENT AND OF POTENTIAL INTEREST TO COMBINE WITH SORAFENIB

Several other agents target angiogenesis and might be useful as combination treatment options for advanced HCC. Two ongoing phase II trials are evaluating the humanized neutralizing anti-VEGF monoclonal antibody bevacizumab in unresectable HCC. Thalidomide also has antiangiogenic properties [80] and has been investigated in pilot studies in combination with capecitabine [81]. Other agents with antiangiogenic effects that might have potential utility in combination therapy for HCC include interferon- α [82] and interleukin-12 [83].

Other targeted signal transduction pathway inhibitors may also be candidates for use in combination therapies for pancreatic cancer, particularly those targeting the epidermal growth factor receptor (EGFR) pathway. EGFR expression is increased in >90% of pancreatic cancer biopsies [84], and is associated with larger tumor size, advanced clinical stage, and poor prognosis [85]. Anti-EGFR monoclonal antibodies (such as cetuximab) have been associated with promising results when used in combination with gemcitabine [86], and could have the potential for use in combination with sorafenib in patients with pancreatic cancers expressing EGFR.

There has been interest in the use of cyclooxygenase (COX)-1 and COX-2 inhibitors in several malignancies, including ovarian carcinoma [87]. These agents have been

shown to block endothelin-1–induced prostaglandin E2 and VEGF release in preclinical models of ovarian cancer [88], and a preclinical study has demonstrated promising effects with the COX-2 inhibitor NS-398 in combination with paclitaxel in an ovarian cancer cell line [89].

Bevacizumab is also under investigation in combination with interferon- α in patients with metastatic malignant melanoma and in combination with imatinib in patients with advanced melanoma or other advanced cancers.

The role of VEGF in gastric cancer provides a rationale for investigating the value of combination therapy with other anti-VEGF approaches. There is also evidence that the EGFR system is involved in regulation of gastric mucosa proliferation and progression of gastric carcinomas [90]. The roles of VEGF and EGFR provide a rationale for investigating combination therapies directed at both of these targets. For example, in preclinical models, the combination of anti-VEGFR and anti-EGFR therapies appeared to be effective in inhibiting gastric cancer growth [91].

Studies of the anti-VEGF agent bevacizumab have revealed promising results in patients with breast cancer, suggesting that targeting angiogenesis could be a useful approach for the treatment of this tumor type. Bevacizumab has been shown to have biological activity in breast cancer both alone and in combination with agents such as capecitabine [92], docetaxel [93], and vinorelbine [94]. These data provide further support for investigating the antiangiogenic properties of sorafenib in patients with breast cancer.

SAFETY AND TOLERABILITY PROFILE OF SORAFENIB IN COMBINATION

The safety and tolerability profile of sorafenib, both as a monotherapy and in a combination approach, has been extensively investigated. Throughout the monotherapy clinical program in patients with mixed solid tumors, including RCC, HCC, and melanoma, commonly reported adverse events associated with sorafenib (400 mg twice daily [bid]) were dermatologic (e.g., hand–foot skin reaction [HFSR] and rash/desquamation), constitutional (e.g., fatigue), and gastrointestinal (diarrhea and nausea) [19, 95–98]. However, most of these toxicities were mild to moderate (grade 1–2) in severity and resolved with appropriate medical intervention or dose reductions/interruptions. Moreover, across the four phase I dose-escalation trials, in patients with a range of tumor types, treatment-emergent hypertension at any grade was observed in only 5%–11% (grade 3–4, 0%–5%) of patients [95–98].

The safety, tolerability, dose-limiting toxicities, and adverse events from combination studies involving sorafenib and chemotherapies or other targeted agents were recently reported in a comprehensive review [99]. Therefore, these

topics are briefly summarized here (Table 1). Studies demonstrated that combinations of sorafenib with chemotherapies or other targeted agents were generally well tolerated. Commonly reported adverse events (dose limiting or grade 3–4) included HFSR, rash, fatigue, neutropenia, and thrombocytopenia in trials in which sorafenib was combined with traditional (or standard) therapies, including interferon- α [36], doxorubicin [55, 57], gemcitabine [63, 64, 68], and DTIC [46, 48, 50]. Although direct comparison of the individual combination trials with monotherapy trials is limited because of differences in study design, enrollment criteria, and patient baseline characteristics, it appears that tolerability profiles were similar to, or slightly higher than, those expected with each therapy alone [19, 48, 100–104]. In contrast, there appeared to be a higher incidence of hypertension with sorafenib combined with the anti-VEGF antibody bevacizumab, which led to the recommendation that sorafenib may have to be administered at the lower dose of 200 mg bid in future investigations of this combination [49]. Overall, it has been previously reported that toxicity profiles observed in combination trials involving cytotoxic chemotherapies rarely overlapped with those associated with sorafenib, suggesting that sorafenib can be successfully combined with a range of therapies [99].

SUMMARY

The MAPK pathway and upregulation of VEGF both play important roles in the growth and maintenance of several solid tumors. Solid tumors frequently exhibit activating oncogenic mutations in *ras* and *b-raf*, and overactivation of Raf-1, resulting in tumor cell proliferation and angiogenesis. The potential benefits of sorafenib in the treatment of solid tumors were supported by preclinical evidence as well as encouraging outcomes in clinical trials of single-agent use, such as in RCC and HCC.

The novel antiproliferative, antiapoptotic, and antiangiogenic mechanisms of action of sorafenib, and its effects on the tumor cell and tumor vasculature, may be particularly valuable when combined with other anticancer agents with complementary or contrasting mechanisms of action. In xenograft models, the combination of sorafenib with gemcitabine, vinorelbine, and irinotecan did not impair efficacy or increase toxicity and was associated with delayed tumor growth compared with the respective monotherapies. These findings provided support for further investigation in clinical trials of sorafenib in combination with a variety of anticancer agents in several tumor types. Taking into consideration the limitations of directly comparing trials that have different enrollment criteria, and that most of the trials presented here are phase I/II, the most promising evidence of antitumor activity was observed with sorafenib com-

bined with interferon- α in RCC [36], DTIC in melanoma [46, 48, 50], doxorubicin in HCC [55], and gemcitabine in ovarian cancer [63, 64, 68]. Moreover, the combination of sorafenib and another targeted agent, bevacizumab, also showed preliminary antitumor activity in patients with ovarian cancer [49]. These encouraging findings warrant further investigation in larger-scale, randomized, controlled trials, comprising combination approaches. These trials also showed that the activity of sorafenib in these tumors may be mediated via effects on Raf kinase, VEGFRs, or both of these. Therefore, there is a continued interest in further investigations of the potential benefits of sorafenib in combination with other anticancer agents to improve outcomes in patients with a variety of solid tumors. Future issues include the optimal combinations, treatment schedules, and dosages of sorafenib combinations for a variety of tumor types. Ongoing clinical trials should also

clarify whether sorafenib combinations offer a PFS and/or survival benefit in patients with advanced cancer.

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