Sorafenib: a multitargeted oral agent for the treatment of advanced renal cell cancer

Sorafenib is a potent, orally active multitargeted kinase inhibitor. *In vitro,* it blocks signaling through several pathways essential for renal cell and other cancers. A large body of evidence has now accrued demonstrating the activity of sorafenib, after immunotherapy failure, in advanced renal cell cancer. Although radiological responses to single-agent sorafenib by standard response evaluation criteria in solid tumors are rare, prolongation of progression-free survival has been demonstrated and is associated with stabilization of anatomically measurable disease. Compared with other available therapies such as cytotoxic chemotherapy and high-dose intravenous interleukin-2, sorafenib is well-tolerated, and studies with this exciting new agent at earlier stages in this fatal disease are awaited.

KEYWORDS: angiogenesis, disease stabilization, PDGFR, Raf, receptor tyrosine kinase, renal cell cancer, VEGFR

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Renal cell cancer (RCC) accounts for approximately 3% of all cancers diagnosed worldwide [1]. Incidental detection has increased the number of patients diagnosed with earlier stage, resectable disease, but a third of these patients will experience recurrence post-operatively [2]. A quarter of patients present with locally advanced or metastatic disease, at which point the response rate to cytotoxic chemotherapy is roughly 4–6% [2], and the median survival approximately 13 months [3]. RCC is increased in patients on long-term immunosuppressant therapy [4], and has occasionally been observed to regress spontaneously [5] and following withdrawal of immunosuppression. For many years, high-dose intravenous interleukin-2 (IL-2) was the standard treatment for metastatic RCC in the USA, having been approved by the US FDA in 1992. Response rates are approximately 21%, with median response durations of up to 54 months being reported [6]. Although high-dose IL-2 can result in prolonged remissions and is the only therapeutic agent with the potential to cure advanced RCC, poor tolerability due to capillary-leak syndrome means that this therapy is not widely available outside specialist centers. IFN-α is much better tolerated, although many patients suffer chronic influenza-like side effects. It has never received US FDA approval, since response rates are 14% and median response duration only 6 months [2]. More recent efforts to improve anti-RCC therapy have focused on rational, targeted treatments including sorafenib, the creation of which has arisen from an understanding of the molecular drivers of RCC.

Hypoxia-inducible factor & receptor tyrosine kinase signaling

Loss of function mutations or silencing of the von Hippel–Lindau gene occur in up to 80% of RCCs [7]. This results in upregulation of the hypoxia-inducible factor (HIF) subunits, HIF-1α and HIF-2α, and thus a constitutively activated hypoxic response. HIF target genes include vascular endothelial-derived growth factor (VEGF) and transforming growth factor-α (TGF-α), both of which signal through receptor tyrosine kinases (RTKs) and are amenable to inhibition with novel therapeutics (Figure 1).

RTKs such as EGFR, HER-2, VEGFR1, 2 and 3, MET and the platelet-derived growth factor receptor (PDGFR-α and -β) are transmembrane proteins that consist of a ligand-binding extracellular domain, a transmembrane protein and an intracellular tyrosine kinase domain [8] (Figure 2). When activated by their ligands, RTKs signal by activating Ras proteins, which cycle between an active, GTP bound, or inactive, GDP bound state. Active Ras localizes the serine/threonine Raf family proteins, including B-Raf and C-Raf, to the cell membrane. Here they act as downstream effectors of Ras signaling by phosphorylating and activating the mitogen-activated protein kinase (MAPK) and the extracellular signal-related kinase (ERK) [9]. Phosphorylation results in ERK dimerization and nuclear translocation, thereby conveying cell surface signals to nuclear transcription factors, which regulate expression of nuclear targets including HIF-1α, and proto-oncogenes such as c-myc and c-fos.

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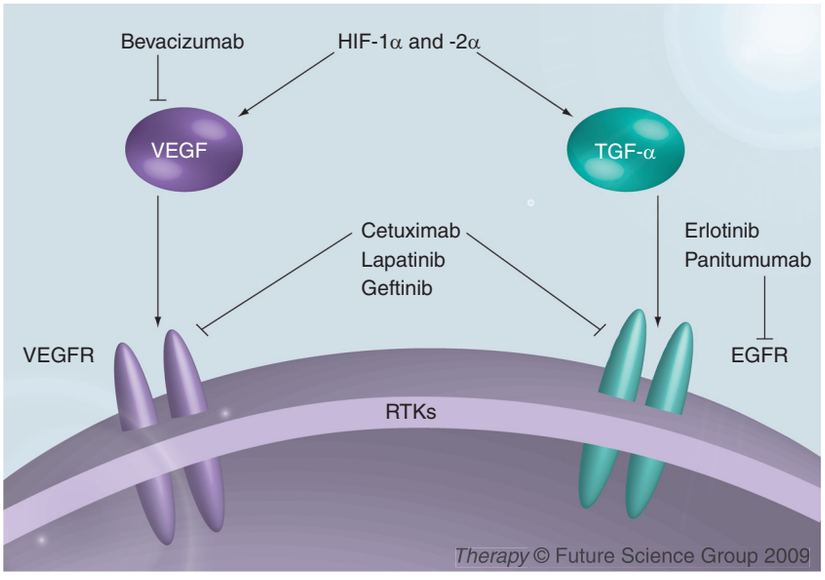

Figure 1. Therapeutic HIF inhibition. EGFR: Endothelial growth factor receptor; HIF: Hypoxia inducible factor; RTK: Receptor tyrosine kinase; TGF: Transforming growth factor; VEGF: Vascular endothelial-derived growth factor; VEGFR: VEGF receptor.

RTKs also activate intracellular phosphatidylinositol 3-kinase (PI3-K), which positively regulates the serine/threonine kinase Akt, thereby activating the mammalian target of rapamyicn (mTOR) through inhibition of the complex formed by the tuberous sclerosis complex proteins [10]. Once activated, mTOR stimulates cell-cycle entry, as well as mRNA translation and stabilization of proteins including HIF-1α [11]. RTK signaling is therefore critical to the regulation of cell growth, differentiation and angiogenesis, and aberrant signaling through receptor tyrosine kinases is a common feature of many solid tumors, including RCC [12]. Pharmacological inhibition of these signaling pathways has been achieved with novel therapeutic agents, and these are increasingly benefiting patients in the clinical setting.

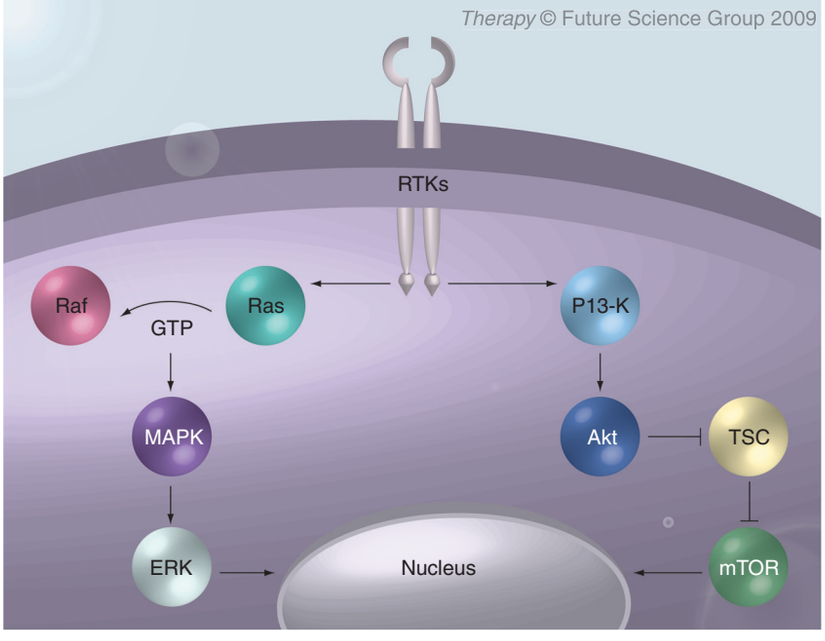

Figure 2. Receptor tyrosine kinase signaling. RTKs signal through MAPK/ERK and PI3-K, as well as a variety of other pathways.
ERK: Extracellular signal-related kinase; GTP: Guanosine triphosphate; MAPK: Mitogen-activated protein kinase; mTOR: Mammalian target of rapamycin; PI3-K: Phosphoinositol 3-kinase; RTK: Receptor tyrosine kinase; TSC: Tuberose sclerosis complex.

Other agents inhibiting RTK signaling

In addition to sorafenib, several other novel therapies targeting RTK signaling have shown activity in RCC, and the clinical trial experience with these agents is briefly described below.

Bevacizumab, a humanized VEGF-neutralizing antibody, has been compared with placebo in a Phase II trial of second-line therapy in 116 patients with metastatic clear-cell RCC. A significant improvement in time to disease progression of 4.8 months was observed for bevacizumab (10 mg/kg), compared with 2.5 months in those treated with placebo (hazard ratio: 2.55; $p < 0.001$). Despite this, the objective response rate to bevacizumab was only 10%, suggesting that this agent stabilized the disease rather than causing anatomical disease regressions. The most common adverse events were hypertension and asymptomatic proteinuria, but there were no grade 4 toxicities or treatment-associated deaths [13]. Bevacizumab given in combination with IFN-α has also been compared with IFN-α alone in a randomized Phase III trial of 649 previously untreated patients with metastatic RCC [14]. The combination prolonged progression-free survival (PFS; 10.2 compared with 5.4 months), but toxicities, particularly fatigue and neutropenia, were more common, and there were three treatment-related deaths due to bleeding and gastrointestinal perforation [15].

Several Phase II trials have investigated the use of drugs inhibiting EGFR, alone and in combination with VEGF inhibition. When the humanized monoclonal EGFR antibody panitumumab was given to 88 patients with metastatic RCC, partial responses were seen in only three patients, but disease stabilization occurred in 50% [16]. The EGFR antagonist, gefitinib, achieved disease stabilization in eight out of 21 metastatic RCC patients [17], but the combination of bevacizumab and the EGFR inhibitor erlotinib failed to show superiority to bevacizumab alone [18].

Temsirolimus, a water-soluble ester of rapamycin and a mTOR inhibitor, has been compared with IFN-α and both drugs combined in a Phase III trial of 626 previously untreated RCC patients with poor prognostic features [19]. Patients treated with temsirolimus alone had improved progression-free (5.5 vs 3.1 months) and overall survival (10.9 vs 7.3 months), together with the lowest toxicities, securing the FDA approval of this drug. Everolimus is an oral mTOR inhibitor that has been compared with best supportive care in a Phase III trial in patients who had progressed within 6 months of treatment with sorafenib (29% of patients), sunitinib (45% of patients) or both (26% of patients). At the second interim analysis, the everolimus group were found to have a 70% greater reduction in disease progression rates than the control group, and a median survival of 4 compared with 2 months [20].

Most recently, several orally administered drugs that, like sorafenib, inhibit multiple kinase pathways, have been tested in the clinical setting. Sorafenib and sunitinib have received US FDA approval for the treatment of metastatic RCC on the basis of Phase III evidence. When compared with subcutaneous IFN-α in 750 patients with previously untreated metastatic RCC, sunitinib extended PFS from 5 to 11 months [21]. An updated analysis of this trial reported that the PFS was unchanged, and that 11 complete responses to sunitinib had occurred compared with four for IFN-α [101]. Adverse events were more common with sunitinib treatment, particularly diarrhea, vomiting, hypertension and hand-foot syndrome. Despite this, quality of life was better in the sunitinib group, probably due to a reduced incidence of fatigue and flu-like symptoms compared with those receiving IFN-α [21]. Pazopanib [22] and axitinib [23] inhibit VEGFR, PDGFR and the stem cell growth factor, c-KIT, and have shown encouraging response rates of approximately 40% in Phase II trials [11]. Both drugs were well-tolerated, the most commonly observed toxicities being hypertension and gastrointestinal side effects, and both are currently being tested in Phase III trials [11].

Sorafenib: chemistry & preclinical experience

Sorafenib (Nexavar®, Bayer Pharmaceuticals Corporation, Leverkusen, Germany/Onyx Pharmaceuticals, CA, USA) is an oral inhibitor of multiple kinase pathways. It targets upstream RTKs, including HIF target genes, but in contrast to the other commercially available multitargeted kinase inhibitors, it also has activity against downstream serine/threonine kinases, including the C-Raf and B-Raf kinases [24]. The chemical name for sorafenib is N-(3-trifluoromethyl-4-chlorophenyl)-N′-(4-(2-methylcarbamoyl pyridine-4-yl)oxyphenyl)urea and the structural formula is shown in Figure 3.

The majority of small-molecule tyrosine kinase inhibitors, known as type I inhibitors, form hydrogen bonds to the ATP-binding site in the kinase domain with the kinase in the 'active conformation'. Structure–activity relationship-guided medicinal chemistry has demonstrated that sorafenib, as well as the bcr/abl tyrosine kinase inhibitor, imatinib, are a different class of kinase inhibitor known as type II. Type II inhibitors bind to the ATP-binding cleft, as well as an adjacent hydrophobic pocket containing a DFG motif, which is present only when the kinase is in an inactive conformation. Due to the additional targeting of the DFG motif, type II inhibitors possess greater cellular potency and selectivity than type I, and this additional hydrophobic-binding domain is likely to be exploited in the design of future generations of kinase inhibitors [25].

Sorafenib was discovered during a screen of medicinal chemistry compounds for *in vitro* activity against recombinant human Raf kinase [26]. Compounds demonstrating Raf kinase inhibition were then tested for inhibition of MAPK and ERK phosphorylation in the human colon cancer cell line, HCT116, which contains a K-Ras mutation. Finally, compounds were tested for antiproliferative effects on HCT116 cells *in vitro* and on soft agar, leading to the identification of sorafenib, previously known as BAY 43–9006, as a potent inhibitor of tumor growth and Raf/MAP/ERK signaling.

Subsequent preclinical evaluation of sorafenib revealed that it also possesses potent activity against a range of upstream tyrosine kinases including VEGFR-2, -3, PDGFR-β, c-KIT and the Fms-like tyrosine kinase-3, which have

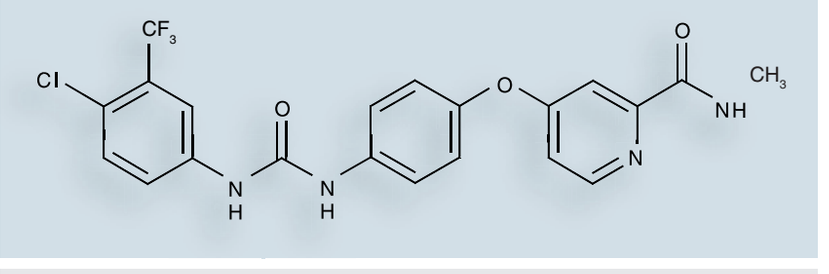

Figure 3. Sorafenib.

Table 1. Pharmacokinetic outcomes in Phase I trials.

Pharmacokinetic parameters	Day	Continuous b.i.d.*				7 days on/7 days off‡				21 days on/7 days off§				28 days on/7 days off¶			
		100 mg	*200 mg*	*400 mg*	*600 mg*	*100 mg*	*200 mg*	*400 mg*	*600 mg*	*100 mg*	*200 mg*	*400 mg*	*600 mg*	*100 mg*	*200 mg*	*400 mg*	*600 mg*
AUC_{0-12} ($mg/h^{-1}/l$)	1	–	–	–	–	6.8	6.1	18.0	21.0	4.8	24.9	24.0	12.0	10.1	10.9	21.8	10.1
	Last	23.8	16.1	71.7	79.6	24.4	19.1	56.6	64.8	30.2	50.5	76.5	77.0	38.1	34.7	47.8	38.1
C_{max} (mg/l)	1	–	–	–	–	1.0	0.8	2.3	2.7	0.7	3.6	3.0	4.6	2.0	1.3	2.9	2.0
	Last	2.31	2.84	9.35	9.81	3.45	2.6	6.2	6.6	4.4	6.3	10.0	9.2	4.7	4.0	5.4	4.7
t_{max} (h)	1	–	–	–	–	6.0	6.0	9.2	6.0	2.5	2.0	3.6	3.6	4.0	5.0	2.9	4.0
	Last	5.2	2.0	3.0	2.5	2.0	2.0	2.0	1.5	2.5	2.0	2.9	2.0	2.0	3.8	12.1	2.0
$t_{1/2}$ (h)		37.9	31.8	28.1	–	38.1	20.1	20.0	24.3	25.2	29.8	23.8	38.6	26.3	31.8	27.4	26.3

*Taken from [28]; †Taken from [30]; ‡Taken from [31]; §Taken from [29].
b.i.d.: Twice daily; $t_{1/2}$: Elimination half-life.

important roles in tumor progression and angiogenesis [24]. Sorafenib has also been shown to have proapoptotic effects by enhancing proteasomal degradation of the antiapoptotic myeloid leukemia-1 protein in several cancer cell lines, including RCC [27]. *In vivo,* activity was demonstrated when sorafenib was administered orally to nude mice bearing breast (MDA-MB-231), colon (COLO-205, HT-29, DLD-1) and non-small-cell lung (NCI-H460, A549) human cancer cell lines as subcutaneous xenografts, with complete tumor stasis being achieved in five of the six models [24]. These results prompted the evaluation of sorafenib in the clinical setting.

Sorafenib: clinical experience

Four Phase I trials of sorafenib were reported in 2005 [28–31]. These were designed to evaluate the safety and tolerability of sorafenib in humans with a variety of advanced solid cancers. In all studies, patients received oral sorafenib at doses ranging from 50 mg once-daily to 800 mg twice-daily (b.i.d.). The treatment regimens tested included a continuous schedule, 7 days of treatment followed by 7 days off-treatment, and either 21 or 28 days on treatment followed by 7 days rest. Only one trial, in which daily b.i.d. treatment was continued until unacceptable toxicity, disease progression or death, systematically examined pharmacodynamic end points [28]. Peripheral blood was taken from patients on days 2 and 7, and then weekly for at least 6 weeks and treated with phorbol-myristate acetate (PMA) that stimulates ERK phosphorylation. T lymphocytes were then stained for MAPK activity and quantified using flow cytometry. In patients receiving 400 mg sorafenib b.i.d., almost complete inhibition of PMA-stimulated ERK phosphorylation was seen by day 21, whilst partial inhibition was seen in patients treated at 200 mg b.i.d. These results were taken to indicate that sorafenib successfully inhibited Raf signaling, but since the IC_{50} for sorafenib-induced Raf inhibition in humans is estimated to be in the millimolar range, it is doubtful whether this assay can be used as an accurate surrogate for Raf activity.

In the Phase I trial carried out by Clark *et al.*, sorafenib was administered in repeated cycles of 7 days on, 7 days off, at doses ranging from 100 mg to 800 mg b.i.d. [30]. Tumor biopsies were taken from some of the patients in this trial and stained immunohistochemically for phospho-ERK. One patient with melanoma, who received sorafenib 600 mg b.i.d., was found to have decreased nuclear phospho-ERK

staining of melanoma cells on day 28 compared with day 1, which correlated with a reduction in [18F] fluorodeoxyglucose uptake on positron emission tomography, as well as a reduction in tumor symptoms. Although this patient's disease subsequently progressed, these findings suggest a correlation between the clinical and biological activity of this drug.

All four Phase I studies aimed to evaluate the pharmacokinetics of oral sorafenib and used mass spectrometry on plasma samples to calculate AUC, C_{max}, t_{max} and elimination half-life ($t_{1/2}$) [28,30]. Mean results for these parameters are summarized in TABLE 1. There was high interpatient variability in C_{max} and AUC [28–31], with no clear relationship to the administered dose [28,30] or drug-related adverse events [29,30]. Time to C_{max} varied between 2.5 and 12 h [28,31], and steady-state concentrations of sorafenib were reached after 7 days of treatment [31]. In the only study to evaluate continuous dosing, maximum mean AUC values were obtained at 600 mg b.i.d., but the difference between 400 and 600 mg b.i.d. was only marginal [28]. Mean $t_{1/2}$ ranged from 20 to 39 h, with substantial plasma accumulation being observed following multiple b.i.d. doses [28–31]. Circulating sorafenib is almost entirely bound to plasma proteins, and its bioavailability was not affected by food intake in these trials [28]. In addition, no clear relationship was demonstrated between sorafenib pharmacokinetics and baseline demographics such as age, gender and body weight [29].

Sorafenib was generally well-tolerated in all four Phase I trials, particularly at doses lower than 400 mg b.i.d. Although most patients reported at least one adverse event, the majority were grade two or lower (89%) [32]. The most common toxicities were fatigue (40%), anorexia (35%), diarrhea (34%), rash (27%), hand-foot syndrome (25%) and stomatitis (9%), and resolved on dose reduction or discontinuation of sorafenib [32]. Grade 3 or 4 toxicities were most commonly rash or hand-foot syndrome (8%), fatigue (6%) and diarrhea (4%), although severe hypertension and alopecia were also occasionally reported [32]. At doses above 400 mg b.i.d., dose reductions were required in up to 75% of patients, and of these patients, 67% experienced dose-limiting toxicities (DLTs) [32]. Across all four trials, DLTs were experienced by six of a total of 13 patients receiving 800 mg b.i.d. [28,30,31], seven out of 39 receiving 600 mg b.i.d. [28,29,31] and only one being treated with sorafenib 400 mg b.i.d. [32]. Three DLTs (fatigue, diarrhea and pancreatitis) were experienced at doses lower than 400 mg b.i.d., and these patients were all in trials in which longer continuous doses of sorafenib were given [28,29]. On the basis of these findings, three of these trials recommended dosing sorafenib at 400 mg b.i.d. [28,29,31], whilst the trial in which sorafenib was administered for 7 days on and 7 days off determined the maximum tolerated dose to be 600 mg b.i.d. [30].

Although none of these trials were powered to evaluate tumor response, preliminary evidence of anti-tumor efficacy was obtained. Across the four trials, 137 patients were analyzed for tumor response by Response Evaluation Criteria in Solid Tumors (RECIST), and 38 of these (28%) had evidence of disease stabilization [32]. Importantly, of the eleven RCC patients enrolled in these trials, five had stable disease. Two of these patients remained stable on sorafenib treatment for over 2 years [28,30], and a third RCC patient was one of only two patients to have an objective partial response [31]. This preliminary evidence of anti-tumor activity, particularly in RCC, together with good tolerability up to the maximum tolerated dose of 400 mg b.i.d., prompted further clinical investigation.

The first Phase II trial of sorafenib was reported in 2006 [33]. This multicenter trial evaluated single-agent sorafenib compared with placebo in patients with a range of tumor types, including RCC. Since sorafenib had been shown to be cytostatic in preclinical studies [24], the trial utilized a randomized discontinuation design that was first proposed in 1975 as a means of detecting disease stabilization [34]. All patients were initially administered sorafenib 400 mg b.i.d., and CT scans were carried out every 12 weeks. Patients with radiological evidence of at least a 25% reduction in disease burden were offered treatment continuation, whilst those with a disease burden within 25% of baseline levels (denoted stable disease) underwent double-blind randomization between sorafenib and placebo. If any patient thus randomized to placebo subsequently progressed, they were rechallenged with sorafenib. In the event of disease progression while taking sorafenib, patients were taken off study.

The primary end point was PFS 12 weeks from randomization, and secondary end points were PFS from the start of treatment, tumor response rate and safety. A total of 502 patients were enrolled over 16 months, of which 202 patients had advanced RCC and all subsequent results discussed relate only to the RCC patients. At 12 weeks, 73 patients (36%) had achieved tumor shrinkage of greater than 25%, 69 (34%)

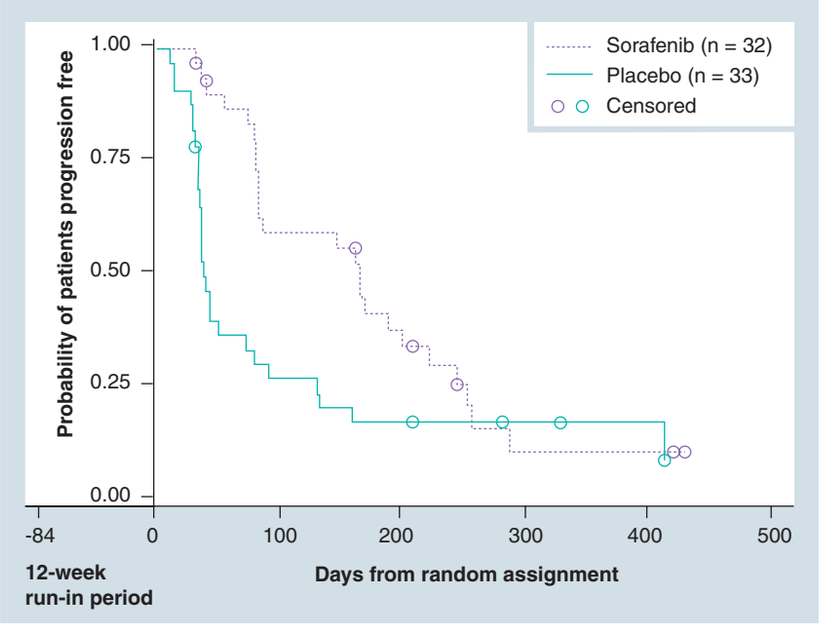

Figure 4. Progression-free survival from 12-week randomization.
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had stable disease and 51 (25%) showed either a greater than 25% increase in tumor size or other evidence or disease progression. Of the 15 patients that discontinued treatment before the 12-week assessment, 12 did so because of adverse events. At 12 weeks post-randomization, 50% of patients receiving sorafenib (16 out of 32) were progression-free, compared with only 18% (six out of 33) receiving placebo. Median PFS postrandomization was also significantly longer in the sorafenib group (24 compared with 6 weeks) (Figure 4). For the entire study, median PFS was 29 weeks, compared with 40 weeks in those patients who continued on sorafenib after the initial 12 weeks. It is notable that, according to WHO criteria, only eight patients in this trial experienced a partial response. In addition, there was no difference in PFS in patients whose tumors shrank by 25–50% compared with those whose tumors shrank by more than 50%, implying that sorafenib prolongs survival by inducing disease stabilization in a majority of treated individuals. In keeping with the Phase I trials, sorafenib was found to be well-tolerated and there were no treatment-related deaths in this study. The majority of adverse events were grade 1 and 2 in severity, the most common at any grade being fatigue (73% of patients), rash and desquamation (66%), hand-foot reaction (62%) and diarrhea (58%). The most common grade 3 or 4 toxicity was hypertension, which was seen in 31% of patients, 46% of whom required antihypertensive therapy.

In 2007, two Phase II trials of sorafenib in combination with IFN-α were reported in the *Journal of Clinical Oncology* [35,36]. Both trials cited the potentially beneficial effect of adding the known anti-angiogenic activity of IFN-α through inhibition of VEGF [37] and basic fibroblast growth factor [37,38] to the VEGF receptor inhibitor actions of sorafenib. Additionally, antiproliferative effects of interferon have been shown to be enhanced in the presence of MAPK/ERK inhibitors [39]. Both trials enrolled patients with metastatic or unresectable RCC. Ryan *et al.* [36] enrolled only patients with clear cell carcinoma who had not received systemic treatments previously, whereas Gollob *et al.* [35] recruited all histological subtypes and allowed any prior systemic therapy except IFN-α. The treatment regimen, which had previously been determined to be well-tolerated in a Phase I trial [40], was similar in both trials, consisting of sorafenib 400 mg orally b.i.d. and IFN-α 10 million units administered subcutaneously on three nonconsecutive days each week, continuing until disease progression or unacceptable toxicity. Response assessment with CT scanning was carried out every 8 weeks. Both trials had response rate as the primary end point, and both evaluated tolerability of the combination.

Response rates were comparable between the two trials and are summarized in Table 2. Gollob *et al.,* noted that out of a total 40 patients, most major responses occurred in patients with clear-cell histology.

The combination of sorafenib with IFN-α seemed to cause more toxicity than sorafenib alone, with Ryan *et al.,* reporting that 77% of patients experienced a grade 3 or worse adverse event and, since the most commonly reported adverse events were fatigue, anorexia, rigors and fever, these were attributed to IFN-α. Diarrhea was also frequent, being reported in 63% of patients, and hand-foot syndrome was seen in 16%. There was one treatment-related death due to severe hypotension following IFN-α. Gollob *et al.* reported toxicities requiring dose modification in 65% of patients, with 28% eventually discontinuing treatment due to adverse events. Fatigue, anorexia, diarrhea, rash and hand-foot syndrome were common.

In concluding their reports, both authors commented on a probable increased response rate in their trials compared with either agent given alone. However, they did express concern at the increased toxicity of the combination of sorafenib and IFN-α. Ryan *et al.* advised caution at overinterpreting the significance of

conventional anatomical markers of response to novel agents such as sorafenib, with which prolongation of survival does not necessarily correlate with reduction in tumor bulk. Another randomized Phase II trial investigated the combination of sorafenib (400 mg b.i.d.) with IFN-α at the slightly lower dose of 9 million units subcutaneously three-times a week or 5 million units five times a week [102]. A total of 100 previously untreated patients with predominantly clear-cell histology were enrolled and tumor responses were similar in the two groups. Overall, partial responses occurred in 30.6% of patients, complete responses in 4.1% and median PFS was 7.9 and 8.5 months in the two groups. Although grade 3 and 4 toxicities were common in both treatment groups, particularly hypophosphataemia (18%), hand-foot syndrome (14%), fatigue (15%) and diarrhea (8%), they were less frequent than had been reported previously.

Sorafenib (400 mg b.i.d.) has also been directly compared with IFN-α (9 million units three-times a week) in a randomized Phase II trial in 189 previously untreated patients with metastatic clear-cell RCC [103]. Disease control rate, defined as the total rate of complete response, partial response and disease stabilization, was greater in the sorafenib arm (79% compared with 64% with IFN-α). Despite this, there was no difference in PFS in the two groups (5.7 and 5.6 months), implying that sorafenib may not have an advantage over IFN-α in treatment-naive patients. Patients who progressed on IFN-α were allowed to cross-over to sorafenib treatment and, in the 50 patients who did so, median PFS was 5.3 months. These results suggest that sorafenib may have most benefit as a second-line treatment after immunotherapy failure.

The Treatment Approaches in RCC Global Evaluation Trial (TARGET), which prompted US FDA approval of sorafenib in RCC, was reported in *The New England Journal of Medicine* in 2007 [41]. In this Phase III trial, 903 patients with advanced RCC were randomized, in a double-blind manner, to receive either continuous treatment with sorafenib 400 mg twice daily or placebo. All patients had progressed after receiving at least one prior treatment, and although the first-line therapy was not specified, most had received immunomodulatory treatments. Tolerability was assessed every 3 weeks for the first 24 weeks and then every 4 weeks, whilst tumor response was evaluated every 6 weeks for the first 24 weeks and every 8 weeks thereafter. Patients were continued on study drug until disease progression or withdrawal due to adverse events or death. Recruitment commenced in November 2003 and, after the discovery of a statistically significant increase in PFS in the sorafenib arm at a planned interim analysis in January 2005 (FIGURE 5C), sorafenib was offered to patients receiving placebo from May 2005.

The primary end point of overall survival was measured from the date of randomization until the date of death. In the first analysis in May 2005, 22% of patients in the sorafenib group and 27% or patients in the placebo group had died. At the final survival analysis 6 months later, a median overall-survival advantage of 19.3 months was seen in the sorafenib group, compared with 15.9 months in the placebo arm, which did not meet statistical significance according to the O'Brien–Fleming rule (FIGURE 5B). A secondary preplanned analysis, which censored data from placebo-treated patients did, however, show a significant overall survival benefit for the sorafenib-treated group [104]. The other co-primary end point of PFS from randomization was determined clinically and radiologically by computed tomography or magnetic resonance imaging, and interpreted according to RECIST criteria by independent radiologists who were blinded to the treatment group. Median PFS was found to be 5.5 months in the sorafenib group, compared with 2.8 months in the placebo group (FIGURE 5D). In keeping with the observation in earlier phase trials that sorafenib prolonged PFS without causing dramatic reductions in measurable disease burden, at the May 2005 cut-off, only one complete response had been seen in a patient receiving sorafenib. Sorafenib also resulted in higher PR rates than placebo (10% compared with 2%) and greater disease stabilization (74% compared with 53%).

Table 2. Efficacy of sorafenib in combination with IFN-α in Phase II trials.

Disease subtype and outcome	Study	
	Ryan et al.* ***(n = 67)***	***Gollob et al.**‡* ***(n = 40)***
Histology	Clear cell	Any
Prior systemic treatment	No	Yes
CR	1%	5%
PR	18%	28%
Unconfirmed PR	11%	N/A
SD	39%	45%
PD	21%	12%
Not assessable	10%	10%
Median PFS	10 months	7 months

**Taken from* [36]*; ‡Taken from* [35]
CR: Complete response; N/A: Not applicable; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; SD: Disease stabilization.

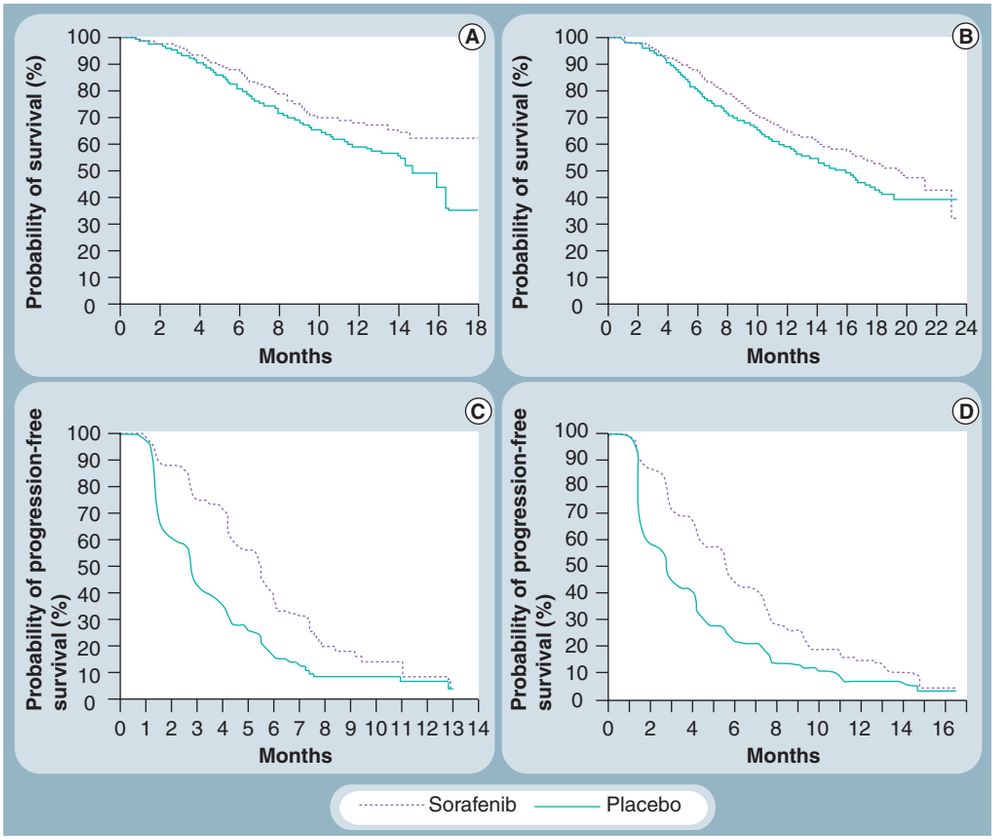

Figure 5. Progression-free & overall survival in the TARGET trial. **(A)** Probability of overall survival in May 2005. **(B)** Probability of overall survival among the same patients in November 2005. **(C)** Probability of progression-free survival among 769 patients in an independent review in January 2005. **(D)** Probability of progression-free survival among all 903 patients in a review by investigators in May 2005.
Taken from [41] with permission.

Adverse events occurred to a similar extent in both treatment groups, and the most common toxicities seen with sorafenib were similar to those seen in Phase II trials, such as hand-foot syndrome and diarrhea. Serious adverse events including cardiovascular events such as hypertension and cardiac ischemia were significantly more common following sorafenib treatment. A total of 46 treatment-associated deaths were reported in the sorafenib group (10% of treated patients), compared with 25 (6%) following placebo treatment. A summary of the toxicity data from published trials of single-agent sorafenib are displayed in TABLE 3. The authors of the TARGET trial deemed that the overall rate of adverse events was low, particularly when compared with cytotoxic agents, and that these toxicities were acceptable in the context of a prolongation of survival in this fatal disease.

Management of toxicity

Compared with traditional cytotoxic anticancer therapies, sorafenib was well-tolerated in the studies described above. Subsequent evaluation through expanded access programs, in which patient selection is less stringent, revealed higher rates of adverse events, with up to 64% of patients experiencing grade 3 and 4 toxicities [42]. They have also identified less clinically apparent toxicities, for example thyroid function abnormalities, which occur in approximately 20% of sorafenib-treated patients, but only rarely require intervention [43]. This is in contrast to sunitinib, which causes biochemical hypothyroidism in 85% of patients [44], highlighting the overlapping but nonidentical kinase inhibitory and toxicity profiles of these multitargeted agents. Since many sorafenib-induced toxicities, such as diarrhea, nausea, vomiting and fatigue, are similar to those caused by chemotherapy, they do not present additional management problems for oncologists. Those highlighted by expanded access programs as being more challenging to control include dermatological complications such as rash, desquamation and the hand-foot syndrome, as well as cardiovascular side effects,

particularly hypertension. Since sorafenib dosing is usually continuous, the management of these side effects is essential to prevent dose reductions or interruptions in therapy.

Dermatological toxicity

The hand-foot syndrome seen with both sorafenib and sunitinib usually appears within 6 weeks of starting treatment, and is often preceded by altered sensation in hands and feet. This is followed by painful, symmetrical erythema and edema. Involved skin can become hyperkeratotic, dry and cracked, particularly over pressure areas and, if left to progress, can become severely disabling. Histologically, keratinocyte maturation appears deregulated with associated inflammatory areas, although the pathogenesis of these changes is not yet well understood [45]. Patients are usually advised to apply moisturizing lotion to affected areas and to wear cotton socks, soft shoes, padded insoles or shock-absorbers, and the use of salicylate-containing creams has also been advised [46]. Symptoms usually resolve completely following dose reduction or discontinuation, and interestingly, although hand-foot syndrome usually recurs when sorafenib is re-introduced, it is often reduced in severity.

Acneiform skin eruptions on the face and upper body are seen with sorafenib, although much less frequently than with EGFR inhibitors. They are frequently preceded by altered scalp sensation, and although they commonly occur at the start of treatment, rashes may disappear spontaneously after a few weeks. The etiology of these rashes remains unclear, although they are hypothesized to relate to inhibition of kinase pathways in the skin. Indeed, there is some evidence that the skin rash seen with the EGFR inhibitors cetuximab and erlotinib correlates with target inhibition and treatment response [47]. Pooled data from four Phase I trials of sorafenib monotherapy suggests that the same is true of sorafenib, since patients in these trials that experienced skin toxicity had a significantly increased time to disease progression compared with those that did not [48]. There is very little evidence available for the management of sorafenib-induced rash, although the use of emollients, hypoallergenic cleansers and avoidance of heat are usually advised. Some advocate the use of antihistamines, antibiotics and the cautious application of topical steroids. Ultimately, dose reductions or discontinuation may become necessary, although the rash also commonly disappears spontaneously [45].

Cardiovascular toxicity

Cardiovascular side effects, particularly hypertension, are frequently problematic with angiogenic inhibitors including sorafenib. In one study of 20 patients given 400 mg sorafenib twice daily, systolic blood pressure increased by at least 10 mmHg in 75% of patients, and diastolic blood pressure increased by 20 mmHg in 60% after only 3 weeks of treatment [49]. This was not associated with a change in secreted humoral factors, and it has been hypothesized that sorafenib-induced hypertension results from changes to the vascular bed or perhaps from endothelial dysfunction. The higher rates of cardiac ischaemia, left ventricular dysfunction and cardiac death seen following sorafenib treatment in the TARGET trial [41], led some to express caution in the use of

Table 3. Toxicity data from published trials of single agent sorafenib.

		Phase I (%)				Phase II (%)	Phase III (%)
		Strumberg et al. [28]	***Moore et al.*** [29]	***Clark et al.*** [30]	***Awada et al.*** [31]	***Ratain et al.*** [33]	***Escudier et al.*** [41]
Grade I/II	Fatigue	33	44	11	43	66	12
	Anorexia	42	29	11	34	44	5
	Diarrhea	32	32	0	16	54	12
	Nausea	30	22	11	11	30	6
	Alopecia	13	17	0	30	53	4
	Rash	26	15	21	32	64	13
	Hand-foot syndrome	17	22	0	32	49	12
Grade III/IV	Fatigue	6	7	10	9	6	5
	Diarrhea	9	0	11	2	4	2
	Alopecia	3	0	0	0	0	<1
	Hand-foot syndrome	6	10	0	11	13	6
	Hypertension	0	0	5	0	31	4

sorafenib, particularly in elderly patients and those with pre-existing cardiac disease. Interestingly, a subset analysis of this trial revealed that cardiac events were actually less common in patients aged over 70 compared with younger patients although the authors point out that the numbers of patients involved were small [50]. It is becoming increasingly apparent that changes in blood pressure with sorafenib therapy are rarely large and that they can be readily managed with standard antihypertensive therapy. Just as for other multitargeted tyrosine kinase inhibitors, all patients receiving sorafenib should have their blood pressure carefully monitored. In fact, in the TARGET subset analysis, outcomes were comparable for older and younger patients, underpinning the role of sorafenib as an effective, well-tolerated agent in a range of patients with advanced RCC.

Current approved indications worldwide

The use of sorafenib in RCC was approved by the US FDA on 20th December 2005 [105] and the EMEA gave marketing authorization on 19th July 2006 [106]. In the UK, the use of targeted therapies in RCC including sorafenib, sunitinib, bevacizumab and temsirolimus is currently under review by The National Institute of Clinical Excellence, and a report is expected in January 2009 [107]. Sorafenib also has activity in hepatocellular cancer, and was granted marketing authorization by the EMEA on 30th October 2007 [108], and US FDA approval on 16th November 2007 [109] for this disease.

Future perspective

Assessing response

Sorafenib usually achieves a survival benefit in association with radiological disease stabilization, as measured by conventional imaging technologies such as CT scanning, and complete radiological responses are rare. This observation calls in to question the value of response assessment criteria such as RECIST in trials of targeted therapies, a problem that was addressed by the use of a randomized discontinuation design in the Phase II trial carried out by Ratain *et al.* [33]. The development of biomarkers that can be used to predict response may address this problem in future. Potential candidates include VEGFR and phospho-ERK, although such strategies have not yet been validated in sufficiently large patient numbers for them to be widely adopted in clinical practice. Advances in imaging technology are also likely to provide novel ways of accurately measuring tumor responsiveness to molecular agents. Potential candidates include the use of ^{18}[F] fluoro-deoxyglucose positron emission tomography to detect changes in the metabolic activity of malignant cells in the absence of gross anatomical changes. Altered blood flow to the tumor would be expected given the activity of sorafenib against VEGFR, which may also be detectable with functional imaging techniques such as dynamic contrast-enhanced MRI.

Optimal dosing

Several of the toxicities induced by sorafenib improve with time, and it has been suggested that gradual dose escalation may enable higher doses to be administered than was possible in the Phase I trials. A multinational Phase II study, sponsored by Bayer, is currently investigating this possibility. Patients with metastatic RCC will receive sorafenib 400 mg b.i.d. for 28 days, escalating to 600 mg b.i.d. for 28 days and then continuing on 800 mg b.i.d. from day 57 onwards, providing no dose-limiting toxicities occur [110]. Treatments will continue until disease progression with response rate as the primary end point. Since some investigators feel that discontinuation of tyrosine kinase inhibitors, for example due to toxicity, can accelerate disease, the results of this trial should inform sorafenib dosing regimes, to maximize therapeutic benefit whilst minimizing unpleasant and disruptive toxicities.

Sequential & combination therapies

The development of sorafenib and other targeted agents with efficacy in RCC, such as bevacizumab and temsirolimus, has arisen from an improved understanding of the molecular pathogenesis of this disease. It is possible that the efficacy of treatment may therefore by improved by inhibiting multiple steps in oncogenic pathways. Since resistance to any anticancer agent must be considered a possibility, the availability of a range of targeted agents is likely to be advantageous, and several studies have looked at their use either in combinations or as sequential therapy.

In one retrospective analysis of patients with advanced RCC who had received sorafenib followed by sunitinib (68 patients) or sunitinib followed by sorafenib (22 patients), PFS and duration of response were comparable in the two groups overall. Interestingly, patients progressing on one agent were frequently observed to undergo partial responses and disease stabilization with the other [111]. A Phase II trial has investigated the use of sunitinib in 61 bevacizumab refractory patients. Of these, 12 patients (23%) had a partial response and 36 (59%) experienced stable

disease [112]. These preliminary results suggest a lack of cross-resistance between angiogenic inhibitors in RCC and a range of trials are currently recruiting patients to investigate various sequential regimes for example temsirolimus versus sorafenib given second-line after sunitinib failure [113].

The use of upfront combinations of these new agents is also being investigated. Most of the completed trials have been early phase dose-escalation studies with safety as the primary end point. The combinations of bevacizumab and the mTOR inhibitors temsirolimus [114] and everolimus [115] were found to be well-tolerated at the standard dose of both drugs. When temsirolimus and sorafenib were given together, severe mucocutaneous toxicitis required dose reduction [116]. Bevacizumab in combination with sorafenib caused grade 3 proteinuria and hypertension precluding administration of sorafenib at doses above 200 mg [51], and bevacizumab and sunitinib given together were also poorly tolerated [117]. Further trials investigating patient outcomes with combination therapies are currently underway.

Adjuvant treatment

The trials described in this review have demonstrated that single-agent sorafenib is a well-tolerated oral agent that stabilizes disease and thereby prolongs PFS in patients with advanced RCC. Nonetheless, cure for these patients remains elusive. In other solid cancers, survival has only been reliably prolonged by improving treatment early in the course of the disease through effective surgery and adjuvant systemic therapy, and the use of sorafenib in the adjuvant setting is being investigated in two international studies. In the USA and Canada, the Eastern Cooperative Oncology Group, Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma trial is currently recruiting patients with potentially surgically curable RCC at high risk of recurrence [118]. Patients are randomized to receive 1 year of sorafenib, sunitinib or placebo starting within 12 weeks postnephrectomy and continuing for 1 year. The primary end point is disease-free survival with patients being stratified based on pathological stage, performance status, histological subtype and whether nephrectomy was open or laparoscopic. In addition, a cardiac substudy will be conducted with patients receiving cardiac function evaluations by Multiple Uptake Gated Acquisition scanning at baseline, and then 3 monthly until the end of treatment. This trial will also seek to determine whether markers predictive of response to sorafenib and sunitinib can be identified from tumor tissue obtained at nephrectomy.

In Europe, the Medial Research Council sponsored SORCE trial is a multicentre Phase III trial investigating adjuvant sorafenib for patients with resected RCC at high or intermediate risk of relapse [119]. In this double-blind study, patients will receive 1 year of sorafenib followed by 2 years placebo, 3 years of sorafenib or 3 years placebo. The primary outcome is metastatis-free survival, defined as time to metastasis or death from primary RCC, while secondary outcomes include overall survival, cost–effectiveness and toxicity. This trial will also attempt to determine biological characteristics of the resected primary including evaluation of sorafenib targets such as von Hippel–Lindau, VEGFR2, FGF2, B-Raf, MEK and ERK and their correlation with patient outcomes. The combined results of these two large trials should provide robust data on the value of sorafenib in the adjuvant setting.

Executive summary

Mechanisms of action

- Sorafenib is a potent small-molecule inhibitor of multiple tyrosine kinases, including vascular endothelial-derived growth factor receptor 2, FLT3, MET, platelet-derived growth factor receptor and FGFR1, as well as the Ras/Raf/MAPK pathway.

Dose administration

- Sorafenib is available as an oral tablet and the recommended dose is 400 mg twice daily.

Clinical efficacy

- Sorafenib causes greater partial response rates than placebo and following immunotherapy in patients with advanced renal-cell cancer but complete responses are rare.
- Sorafenib maintains stable disease in the majority of patients treated.
- Sorafenib prolongs progression-free survival compared with placebo and following IFN-α, despite this lack of anatomical response assessed by response evaluation criteria in solid tumors.

Tolerability

- Sorafenib is generally better tolerated than cytotoxic chemotherapy and intravenous interleukin 2.
- The most common side effects of fatigue, diarrhea and hand-foot syndrome are usually mild.
- Severe toxicities, including hypertension, are rare.

Conclusion

Sorafenib is an exciting new oral agent that potently inhibits signaling through multiple kinase pathways that are important in renal cell and other cancers. It is well-tolerated and has demonstrated activity in metastatic RCC that translates into a survival advantage compared with placebo, even at advanced stages of the disease. It is currently indicated as a second-line treatment after failure of immunotherapy. Potentially, use at earlier stages and in combination with some of the many new targeted agents is likely to continue to improve the prognosis for people with RCC without significantly increasing toxicity. If we are to derive the maximum amount of information regarding the mechanisms of action of these targeted therapies, it is essential that trials are designed to evaluate biological and functional radiological end points, in addition to traditional outcome measures such as survival.

Financial & competing interests disclosure

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Bibliography

Papers of special note have been highlighted as:
▪ of interest ▪▪ of considerable interest

1 Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C: Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. *Cancer Treat. Rev.* 34, 193–205 (2008).

2 Cohen HT & McGovern FJ: Renal-cell carcinoma. *N. Engl. J. Med.* 353, 2477–2490 (2005).

3 Bracarda S, Caserta C, Sordini L *et al.*: Protein kinase inhibitors in the treatment of renal cell carcinoma: sorafenib. *Ann. Oncol.* 18(Suppl. 6), 22–25 (2007).

4 Muruve NA & Shoskes DA: Genitourinary malignancies in solid organ transplant recipients. *Transplantation* 80, 709–716 (2005).

5 Snow RM & Schellhammer PF: Spontaneous regression of metastatic renal cell carcinoma. *Urology* 20, 177–181 (1982).

6 Yang JC, Sherry RM, Steinberg SM *et al.*: Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. *J. Clin. Oncol.* 21, 3127–3132 (2003).

7 Yao M, Yoshida M, Kishida T *et al.*: VHL tumor suppressor gene alterations associated with good prognosis in sporadic clear-cell renal carcinoma. *J. Natl. Cancer Inst.* 94, 1569–1575 (2002).

8 Li E & Hristova K: Role of receptor tyrosine kinase transmembrane domains in cell signaling and human pathologies. *Biochemistry* 45, 6241–6251 (2006).

9 Schlessinger J: Cell signaling by receptor tyrosine kinases. *Cell* 103, 211–225 (2000).

10 Cho D, Signoretti S, Regan M, Mier JW, Atkins MB: The role of mammalian target of rapamycin inhibitors in the treatment of advanced renal cancer. *Clin. Cancer Res.* 13, 758s–763s (2007).

11 Costa LJ & Drabkin HA: Renal cell carcinoma: new developments in molecular biology and potential for targeted therapies. *Oncologist* 12, 1404–1415 (2007).

12 Lengyel E, Sawada K & Salgia R: Tyrosine kinase mutations in human cancer. *Curr. Mol. Med.* 7, 77–84 (2007).

13 Yang JC, Haworth L, Sherry RM *et al.*: A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N. Engl. J. Med.* 349, 427–434 (2003).

14 Escudier B, Pluzanska A, Koralewski P *et al.*: Bevacizumab plus interferon α-2a for treatment of metastatic renal cell carcinoma: a randomized, double-blind Phase III trial. *Lancet* 370, 2103–2111 (2007).

15 Frampton JE & Keating GM: Bevacizumab: in first-line treatment of advanced and/or metastatic renal cell carcinoma. *BioDrugs* 22, 113–120 (2008).

16 Rowinsky EK, Schwartz GH, Gollob JA *et al.*: Safety, pharmacokinetics, and activity of ABX-EGF, a fully human anti-epidermal growth factor receptor monoclonal antibody in patients with metastatic renal cell cancer. *J. Clin. Oncol.* 22, 3003–3015 (2004).

17 Dawson NA, Guo C, Zak R *et al.*: A Phase II trial of gefitinib (Iressa, ZD1839) in stage IV and recurrent renal cell carcinoma. *Clin. Cancer Res.* 10, 7812–7819 (2004).

18 Bukowski RM, Kabbinavar FF, Figlin RA *et al.*: Randomized phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in metastatic renal cell cancer. *J. Clin. Oncol.* 25, 4536–4541 (2007).

19 Hudes G, Carducci M, Tomczak P *et al.*: Temsirolimus, interferon α, or both for advanced renal-cell carcinoma. *N. Engl. J. Med.* 356, 2271–2281 (2007).

20 Motzer RJ, Escudier B, Oudard S *et al.*: Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomized, placebo-controlled Phase III trial. *Lancet* 372, 449–456 (2008).

21 Motzer RJ, Hutson TE, Tomczak P *et al.*: Sunitinib versus interferon α in metastatic renal-cell carcinoma. *N. Engl. J. Med.* 356, 115–124 (2007).

22 Sonpavde G, Hutson TE, Sternberg CN: Pazopanib, a potent orally administered small-molecule multitargeted tyrosine kinase inhibitor for renal cell carcinoma. *Exp. Opin Invest. Drugs* 17, 253–261 (2008).

23 Rixe O, Bukowski RM, Michaelson MD *et al.*: Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a Phase II study. *Lancet Oncol.* 8, 975–984 (2007).

24 Wilhelm SM, Carter C, Tang L *et al.*: BAY 43–9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res.* 64, 7099–7109 (2004).

▪▪ **Extensive preclinical evaluation of the mode of action of sorafenib.**

25 Liu Y & Gray NS: Rational design of inhibitors that bind to inactive kinase conformations. *Nat. Chem. Biol.* 2, 358–364 (2006).

26 Lyons JF, Wilhelm S, Hibner B, Bollag G: Discovery of a novel Raf kinase inhibitor. *Endocr. Relat. Cancer* 8, 219–225 (2001).

▪ **Description of the discovery of sorafenib.**

27 Yu C, Bruzek LM, Meng XW *et al.*: The role of Mcl-1 downregulation in the proapoptotic activity of the multikinase inhibitor BAY 43–9006. *Oncogene* 24, 6861–6869 (2005).

28 Strumberg D, Richly H, Hilger RA *et al.*: Phase I clinical and pharmacokinetic study of the Novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43–9006 in patients with advanced refractory solid tumors. *J. Clin. Oncol.* 23, 965–972 (2005).

29 Moore M, Hirte HW, Siu L *et al.*: Phase I study to determine the safety and pharmacokinetics of the novel Raf kinase and VEGFR inhibitor BAY 43–9006, administered for 28 days on/7 days off in patients with advanced, refractory solid tumors. *Ann. Oncol.* 16, 1688–1694 (2005).

30 Clark JW, Eder JP, Ryan D, Lathia C, Lenz HJ: Safety and pharmacokinetics of the dual action Raf kinase and vascular endothelial growth factor receptor inhibitor, BAY 43–9006, in patients with advanced, refractory solid tumors. *Clin. Cancer Res.* 11, 5472–5480 (2005).

31 Awada A, Hendlisz A, Gil T *et al.*: Phase I safety and pharmacokinetics of BAY 43–9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumors. *Br. J. Cancer* 92, 1855–1861 (2005).

32 Strumberg D, Clark JW, Awada A *et al.*: Safety, pharmacokinetics, and preliminary antitumor activity of sorafenib: a review of four phase I trials in patients with advanced refractory solid tumors. *Oncologist* 12, 426–437 (2007).

33 Ratain MJ, Eisen T, Stadler WM *et al.*: Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* 24, 2505–2512 (2006).

▪▪ **Phase II trial of sorafenib utilizing a randomized discontinuation design.**

34 Amery W & Dony J: A clinical trial design avoiding undue placebo treatment. *J. Clin. Pharmacol.* 15, 674–679 (1975).

35 Gollob JA, Rathmell WK, Richmond TM *et al.*: Phase II trial of sorafenib plus interferon α-2b as first- or second-line therapy in patients with metastatic renal cell cancer. *J. Clin. Oncol.* 25, 3288–3295 (2007).

36 Ryan CW, Goldman BH, Lara PN, Jr. *et al.*: Sorafenib with interferon α-2b as first-line treatment of advanced renal carcinoma: a phase II study of the Southwest Oncology Group. *J. Clin. Oncol.* 25, 3296–3301 (2007).

37 von Marschall Z, Scholz A, Cramer T *et al.*: Effects of interferon α on vascular endothelial growth factor gene transcription and tumor angiogenesis. *J. Natl Cancer Inst.* 95, 437–448 (2003).

38 Singh RK, Gutman M, Bucana CD *et al.*: Interferons α and β down-regulate the expression of basic fibroblast growth factor in human carcinomas. *Proc. Natl Acad. Sci. USA* 92, 4562–4566 (1995).

39 Romerio F, Zella D: MEK and ERK inhibitors enhance the anti-proliferative effect of interferon-α2b. *Faseb J.* 16, 1680–1682 (2002).

40 Escudier B, Lassau N, Angevin E *et al.*: Phase I trial of sorafenib in combination with IFN α-2a in patients with unresectable and/or metastatic renal cell carcinoma or malignant melanoma. *Clin. Cancer Res.* 13, 1801–1809 (2007).

41 Escudier B, Eisen T, Stadler WM *et al.*: Sorafenib in advanced clear-cell renal-cell carcinoma. *N. Engl. J. Med.* 356, 125–134 (2007).

▪▪ **Phase III trial demonstrating improved survival with sorafenib compared with placebo in advanced renal-cell cancer.**

42 Riechelmann RP, Chin S, Wang L *et al.*: Sorafenib for metastatic renal cancer: the Princess Margaret experience. *Am. J. Clin. Oncol.* 31, 182–187 (2008).

43 Tamaskar I, Bukowski R, Elson P *et al.*: Thyroid function test abnormalities in patients with metastatic renal cell carcinoma treated with sorafenib. *Ann. Oncol.* 19, 265–268 (2008).

44 Rini BI, Tamaskar I, Shaheen P *et al.*: Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. *J. Natl Cancer Inst.* 99, 81–83 (2007).

45 Robert C, Soria JC, Spatz A *et al.*: Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol.* 6, 491–500 (2005).

46 Porta C, Paglino C, Imarisio I, Bonomi L: Uncovering Pandora's vase: the growing problem of new toxicities from novel anticancer agents. The case of sorafenib and sunitinib. *Clin. Exp. Med.* 7, 127–134 (2007).

47 Perez-Soler R, Saltz L: Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? *J. Clin. Oncol.* 23, 5235–5246 (2005).

48 Strumberg D, Awada A, Hirte H *et al.*: Pooled safety analysis of BAY 43–9006 (sorafenib) monotherapy in patients with advanced solid tumors: Is rash associated with treatment outcome? *Eur. J. Cancer* 42, 548–556 (2006).

49 Veronese ML, Mosenkis A, Flaherty KT *et al.*: Mechanisms of hypertension associated with BAY 43–9006. *J. Clin. Oncol.* 24, 1363–1369 (2006).

50 Eisen T, Oudard S, Szczylik C *et al.*: Sorafenib for older patients with renal cell carcinoma: subset analysis from a randomized trial. *J. Natl Cancer Inst.* 100, 1454–1463 (2008).

51 Azad NS, Posadas EM, Kwitkowski VE *et al.*: Combination targeted therapy with sorafenib and bevacizumab results in enhanced toxicity and antitumor activity. *J. Clin. Oncol.* 26, 3709–3714 (2008).

Websites

101 Sunitinib versus interferon (IFN)-α as first-line treatment of metastatic renal cell carcinoma
www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=32895

102 Two schedules of sorafenib daily and interferon-α2a (IFN) in metastatic renal cell carcinoma
www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=54&abstractID=20356

103 First-line treatment with sorafenib versus interferon
www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=34559

104 Final results of the randomized Phase III trial of sorafenib in advanced renal cell carcinoma
http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/5023?maxtoshow=&HITS=20&hits=20&RESULTFORMAT=&fulltext=final+results+of+the+randomized+phase+III+trial+of+sorafenib+in+advanced+renal+cell+carcinoma&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT

105 FDA approval for sorafenib in the treatment of renal cell cancer
www.cancer.gov/cancertopics/druginfo/fda-sorafenib-tosylate#Anchor-Kidne-39939.

106 Orphan designation by the European for sorafenib for the treatment of renal cell carcinoma
www.emea.europa.eu/pdfs/human/comp/opinion/029404en.pdf

107 NICE guidance on the use of bevacizumab, sorafenib, sunitinib and temsirolimus in renal cell cancer
www.nice.org.uk/guidance/index.jsp?action=byID&o=11817

108 Orphan designation by the European for sorafenib for the treatment of hepatocellular carcinoma
www.emea.europa.eu/pdfs/human/comp/opinion/9526906en.pdf

109 FDA approval for sorafenib in the treatment of hepatocellular carcinoma
www.fda.gov/cder/Offices/OODP/whatsnew/sorafenib.htm

110 Trial of sorafenib dose escalation in renal cell carcinoma
http://clinicaltrials.gov/ct2/show/NCT00618982?intr=%22Sorafenib%22&rank=21

111 Sequential use of sorafenib and sunitinib
www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=32197

112 Sunitinib in bevacizumab-refractory metastatic renal cell carcinoma
www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=31860

113 Temsirolimus versus sorafenib as second-line therapy in patients with advanced RCC who have failed first-line sunitinib
http://clinicaltrials.gov/ct2/show/NCT00474786

114 Phase I/II trial of the mTOR inhibitor, CCI-779 and bevacizumab
www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=30961

115 Phase II study of bevacizumab and everolimus
www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=34991

116 Sorafenib combination with temsirolimus in patients with advanced solid malignancies
www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=31401

117 Phase I trial of bevacizumab plus sunitinib
www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=32187

118 Sunitinib or sorafenib in the adjuvant treatment of patients with kidney cancer
http://clinicaltrials.gov/ct/gui/show/NCT00326898?order=1

119 SORCE: A Phase III randomised controlled study comparing sorafenib with placebo in patients
www.ctu.mrc.ac.uk/studies/RE05.asp