Sorafenib tosylate in advanced kidney cancer: past, present and future

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The objective of this paper was to review the development of sorafenib tosylate in kidney cancer. The MedLine database, the Proceedings of the Annual American Society of Clinical Oncology meeting, as well as those of other key international meetings were extensively searched to identify relevant publications. Furthermore, the authors' direct experience with the drug was taken into account when commenting on the results retrieved. Sorafenib is a multikinase inhibitor that targets VEGF and PDGF receptors, other kinases, as well as the serine–threonine kinase Raf. Following early signs of activity from phase I and II studies, it has been shown to improve survival of pretreated advanced kidney cancer patients within a placebo-controlled, randomized, phase III trial, leading to its approval both in the United States and in Europe. Its activity has been subsequently confirmed in a real-world population by two expanded access programs performed globally, but not in a first-line setting; it also proved to be non-cross-resistant with two other molecularly targeted agents. Finally, its toxicity profile, which is acceptable and highly predictable, makes sorafenib appealing for combination treatments, especially with other molecularly targeted agents. Despite having been already demonstrated to be active in kidney cancer, the exact role of sorafenib in the first-line setting, in patients who have failed other molecularly targeted agents, and especially in combination with other agents, deserves further, prospective, studies. *Anti-Cancer Drugs* **20:409–415 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Sorafenib tosylate (BAY 43-9006, Nexavar; Bayer Schering Pharma, Berlin, Germany) [1], whose chemical structure is shown in Fig. 1, was originally identified during the screening of compounds able to inhibit the serine–threonine kinase Raf (with its three isoforms, A-Raf, B-Raf, and Raf1 or C-Raf), the first kinase along the so-called mitogen-activated protein kinase (MAPK) pathway (Fig. 2) and a key regulator of cell proliferation and survival [2]; furthermore, wild-type Raf1 can also prolong cell survival, independent of MAPK signaling, by direct interaction with antiapoptotic and apoptotic regulatory proteins [3].

Later, the activity of sorafenib on several tyrosine kinases involved in tumor angiogenesis was demonstrated. Indeed, sorafenib is able to inhibit, at pharmacological concentrations, kinases such as VEGFR-2, VEGFR-3, PDGFR-β, c-KIT, Flt-3, FGFR1, and RET (Table 1).

Thus, sorafenib exerts its antitumor activity by inhibiting both cell proliferation (through its activity on Raf kinase) and angiogenesis (through its activity on VEGFR-2 and VEGFR-3 and PDGFR-β), acting on tumor cells as well as endothelial cells and pericytes [4,5] (Fig. 3).

If, on the one hand, sorafenib's antiangiogenic properties are evident in all the tumor models studied so far, its inhibitory activity on the MAPK pathway seems to be more or less important depending on the type of tumor considered. For example, the MAPK pathway seems to be extremely important in hepatocellular carcinoma (HCC) [6], whereas its relevance in kidney cancer has yet to be precisely defined [4].

Summary of phase I studies of sorafenib

A total of four single-agent phase I trials [7–10] evaluating different sorafenib doses and schedules have been performed (Table 2). From these studies, the continuous oral administration of sorafenib at the dose of 400 mg twice daily (b.i.d.) emerged as the schedule recommended for the future development of the drug. Dose-limiting toxicities in these studies included grade 3 diarrhea and fatigue at 800 mg b.i.d., and grade 3 skin toxicity at 600 mg b.i.d. Overall, sorafenib was well tolerated and the majority of adverse events were mild-to-moderate in severity and easily manageable. In these phase I trials, 11 patients with metastatic renal cell carcinoma (RCC) were evaluated for tumor response (using Response Evaluation Criteria in Solid Tumors).

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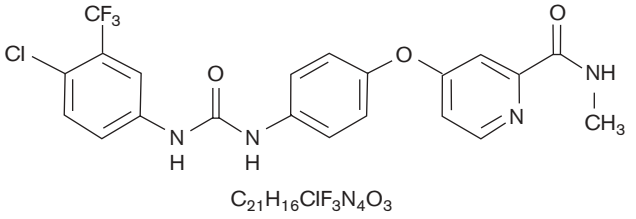
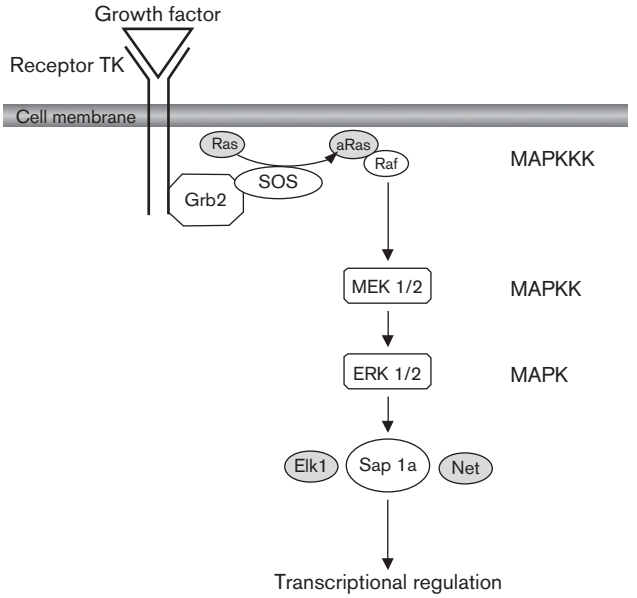
Fig. 1



Chemical structure of sorafenib.

Fig. 2



Schematic representation of the mitogen-activated protein kinase (MAPK) pathway.

Table 1 Kinase (tyrosine as well as serine–threonine) inhibition by sorafenib

Kinase	Sorafenib, IC_{50} (μmol/l)
VEGFR-2	0.030–0.090
VEGFR-3	0.020–0.100
PDGFR-β	0.057–0.080
c-KIT	0.068
Flt-3	0.020–0.058
FGFR-1	0.58
EGFR	>100
c-Met	>100
IGFR-1R	>100
Raf-1	0.006

IC_{50}, median inhibition concentration.

Early signals of antitumor activity were detected in one patient with metastatic RCC who, having been treated with sorafenib 600 mg b.i.d., had a sustained (104 days) confirmed partial response (PR), as well as in two additional RCC patients who experienced sustained (≥ 2 years) stable disease. Notably, another PR was observed in a HCC patients.

Proof of principle of sorafenib activity in renal cell carcinoma: results of a randomized discontinuation trial

The safety and efficacy of sorafenib for the treatment of patients with advanced cancer were first studied within a phase II trial that was designed according to a discontinuation randomization trial (RDT) design. The RDT (or withdrawal) design attempts to assess the clinical activity of a drug while minimizing the use of placebo [11]; in such a trial, all patients receive the study drug for an initial run-in period, followed by random assignment of potential responders to either the study drug or placebo. The design of the sorafenib RDT is reported in Fig. 4.

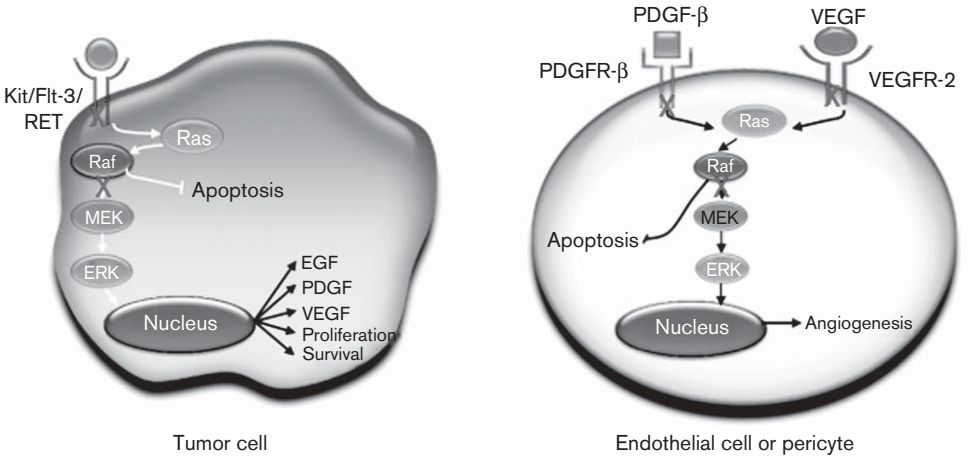
Originally, the study focused on patients with colorectal cancer, but allowed enrolment of patients with other solid tumor types. During the course of the study, evidence of tumor regression in many patients with RCC led to a protocol amendment, which extended recruitment of patients with RCC and terminated enrolment of patients with colorectal cancer. At the end of the study, 202 out of 502 patients had RCC.

Of the 202 RCC patients treated during the run-in period, 73 patients had tumor shrinkage of $\geq 25\%$. Sixty-five patients with stable disease at 12 weeks were randomly assigned to sorafenib ($n = 32$) or placebo ($n = 33$). At 24 weeks, 50% of the sorafenib-treated patients were progression-free versus 18% of the placebo-treated patients ($P = 0.0077$); median progression-free survival (PFS) from randomization was significantly longer with sorafenib (24 weeks) than placebo (6 weeks; $P = 0.0087$). Median overall PFS was 29 weeks for the entire RCC population ($n = 202$). Sorafenib was readministered in 28 patients whose disease progressed on placebo; these patients continued on sorafenib, until further progression, for a median of 24 weeks.

Regarding sorafenib tolerability, common adverse events were as expected from earlier phase I studies and included skin rash/desquamation, hand–foot skin reaction, and fatigue; 9% of patients discontinued therapy and no patients died from toxicity.

The results of this placebo-controlled phase II study [12] clearly demonstrated that sorafenib had significant activity in metastatic RCC; additional evidence for antitumor activity was provided by the restabilization of the disease in patients whose tumor had progressed on placebo and were switched to sorafenib.

Fig. 3



Sorafenib exerts its antitumor activity by inhibiting both cell proliferation (through its activity on Raf kinase) and angiogenesis (through its activity on VEGFR-2 and VEGFR-3 and PDGFR-β), acting both on tumor cells as well as on endothelial cells and pericytes.

Table 2 Summary of the four sorafenib phase I studies

	Objective response (RECIST)				
Study	Evaluable patients (*n*)	Partial response (*n*)	Stable disease (*n*)	Progressive disease (*n*)	Median TTP (days)
1	19		5	14	42
2	32	1	16	15	69
3	41		9	32	63
4	44	1	25	18	83
Overall	136	2	55 (40.4%)	79	64.2

RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time-to-progression.

Furthermore, the median duration of sorafenib treatment in these patients after crossover was comparable with the median PFS for patients randomly assigned to placebo, suggesting that patients were not disadvantaged from a brief period of placebo treatment [12].

Phase III registrative trial of sorafenib in renal cell carcinoma: the Treatment Approaches in Renal Cancer Global Evaluation Trial study

The Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) study was a large, registrative phase III, multicenter, randomized, placebo-controlled trial in which 903 patients with clear-cell RCC that was resistant to standard therapy (mainly, but not only, immunotherapy) were randomized to receive either continuous treatment with oral sorafenib (at the classical dose of 400 mg b.i.d.) or placebo. The design of the study is summarized in Fig. 5.

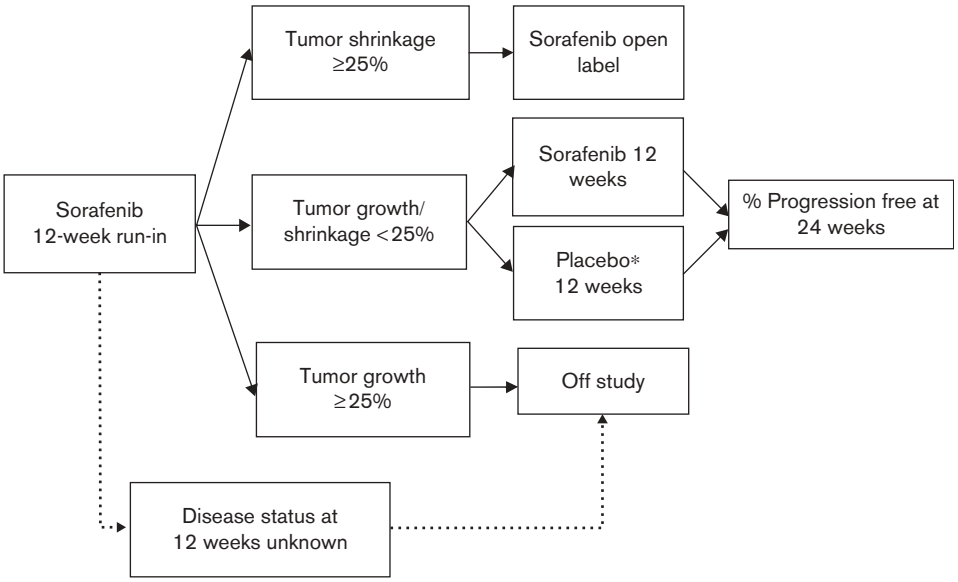
Even though the primary endpoint of the study was overall survival (OS), a single planned analysis of PFS, performed in January 2005, showed a statistically significant benefit of sorafenib over placebo [13]; consequently, crossover was permitted from placebo to sorafenib, beginning in May 2005. On account of crossover, 48% of the patients originally randomized to receive placebo received sorafenib instead.

At the January 2005 cutoff, the median PFS was 5.5 months in the sorafenib group and 2.8 months in the placebo group [hazard ratio (HR) for disease progression in the sorafenib group: 0.44, $P < 0.01$] [13,14].

OS analysis before crossover showed an estimated 39% improvement for sorafenib versus placebo (HR = 0.71; $P = 0.015$); a subsequent intention-to-treat analysis, performed 6 months after crossover, including patients ($n = 216$) who had crossed over to sorafenib, showed a 30% improvement in OS for sorafenib versus placebo (HR = 0.77; $P = 0.015$). Prespecified O'Brien–Fleming statistical boundaries were not reached by these OS differences [15,16]. Final OS at 561 deaths showed a nonsignificant improvement of 13.5% for sorafenib versus placebo (median 17.8 vs. 15.2 months; HR = 0.88; $P = 0.146$). However, a preplanned secondary analysis censoring placebo data, to avoid the confounding effect of crossover, was then performed. A significant OS benefit for sorafenib versus placebo was thus seen (HR = 0.78, 95% confidence interval = 0.62, 0.97; $P = 0.0287$) [16]. A summary of these OS analyses is reported in Table 3.

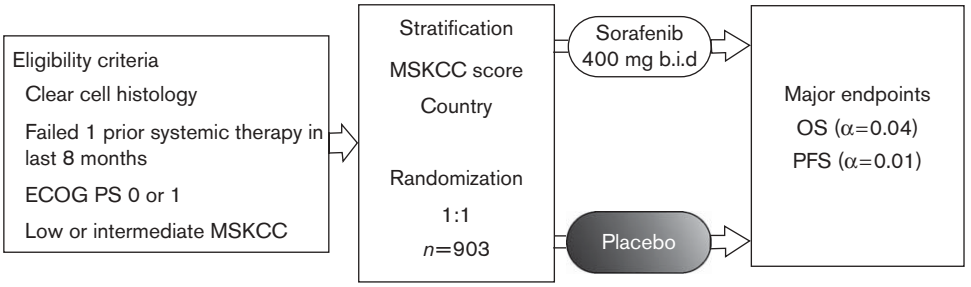
Regarding tumor response assessment, 84% of the 451 sorafenib-treated patients had a clinical benefit (< 1% had a complete response, 10% had a PR, and 74% had stable disease), whereas among the 452 patients randomized to receive placebo 55% had a clinical benefit (2% had a PR and 53% had stable disease) [14].

Fig. 4



Randomized discontinuation trial design and patients allocation. *Placebo patients who progressed could cross over to sorafenib.

Fig. 5



Registrative, randomized, placebo-controlled phase III Treatment Approaches in Renal Cancer Global Evaluation Trial study design. b.i.d., twice daily; ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center; OS, overall survival; PFS, progression-free survival.

Table 3 Overall survival analysis of the registrative TARGET study over time

	OS at crossover	OS 6 months postcrossover	OS 6 months postcrossover with placebo censored
Placebo OS (months)	14.7	15.9	14.3
Sorafenib OS	Not reached	19.3	19.3
Hazard ratio	0.72	0.77	0.74
P value	0.018	0.015	0.01
O'Brien–Fleming stopping boundary	0.0005	0.0094	NA

OS, overall survival; TARGET, Treatment Approaches in Renal Cancer Global Evaluation trial.

In respect to tolerability, adverse events occurring during sorafenib treatment were predominantly of grade 1 or 2; however, sorafenib-induced side effects are extremely peculiar [17] and if not promptly recognized and adequately treated, they could progress to higher grades and have a negative impact on patients' everyday lives.

Among the most common side effects reported within the TARGET study were diarrhea, skin rash, fatigue, hand–foot skin reaction, alopecia, nausea, and hypertension. The most common laboratory abnormalities included lymphopenia, hypophosphatemia, and elevated lipase levels [14].

Sorafenib in everyday clinical practice: results of the global expanded access programs

The antitumor activity of sorafenib, as well as its safety, were confirmed by the results of the two expanded access

Table 4 Summary of the results of the two global expanded access programs of sorafenib in advanced RCC

	Advanced renal cell carcinoma sorafenib study (ARCCS-EU)	Advanced renal cell carcinoma sorafenib study (USA)
Overall response rate (%)	1.8	4
Stable disease $\geq$ 8 weeks (%)	71	80
Progression-free survival (months)	6.8	7.0

EU, European Union; RCC, renal cell carcinoma.

programs (EAPs), performed in the European Union (EU) [18] and in the United States [19]. These results are summarized in Table 4.

The results of the two EAPs are extremely important, as patients treated within them are representative of a broader range of RCC patients in the community than those, inevitably more selected (and thus biased), enrolled into the registrative TARGET study.

Notably, both response rates and toxicities observed in the EAPs were similar to those reported in the phase III TARGET study [18,19]; furthermore, sorafenib also proved to be active and tolerable in very peculiar (and previously untested) patient populations, including patients with nonclear-cell histology, patients with brain metastases (where the drug proved to be manageable without an excess risk of cerebral hemorrhages [20], despite early concerns [21]), patients previously treated with other antiangiogenic agents, and elderly (> 65 years of age) patients.

Approval status

Sorafenib was approved by the US Food and Drug Administration on 20 December 2005 for the treatment of RCC as a whole (i.e. without indications relative to the line of treatment), and received an EU marketing authorization for the treatment of advanced kidney cancer patients refractory to, or unsuitable for, cytokine therapy, on 19 July 2006.

More recently, the European Commission granted marketing authorization to sorafenib tablets for the treatment of patients with HCC, after the presentation of the SHARP (Sorafenib HCC Assessment Randomized Protocol) study [22] on 30 October 2007.

Open questions: first-line treatment

The activity of sorafenib in first-line in RCC has been investigated within a randomized phase II study, where sorafenib was evaluated head-to-head with interferon-α [23].

The design of the study allowed a dose escalation of sorafenib to 600 mg b.i.d., or the crossover from Interferon to sorafenib upon disease progression, depending on the original randomization arm.

Surprisingly, the study demonstrated no significant differences in terms of PFS (i.e. the primary endpoint of the study) between the two arms: 5.7 versus 5.6 months for sorafenib and interferon, respectively; despite this, disease control rate (objective response plus stable disease) and overall quality of life favored sorafenib, whereas the overall incidence of side effects was similar between the two treatment arms.

Notably, in the second part of the study (i.e. after first progression), median PFS was 5.3 months for those patients who crossed from interferon to sorafenib, whereas it was 3.6 for those who dose escalated sorafenib to 600 mg b.i.d., a dose that proved to be well-tolerated.

This study has been criticized on account of the presence, in both arms, of a large number of patients with particularly advanced disease (as demonstrated by the average number of metastatic sites), a feature that could have had an impact on the results of the study.

Open questions: activity in patients already treated with molecularly targeted agents

Three molecularly targeted agents proved able to positively impact in either PFS or OS in previously untreated RCC patients, that is, sunitinib [24], bevacizumab (+ interferon) [25], and temsirolimus [26], the latter only in patients with particularly poor prognostic features.

Despite the activity of these agents, patients ultimately progress, making essential the identification of treatment that could be active also after a first-line use of a molecularly targeted agent. In addition to the positive results of the recent placebo-controlled, randomized trial of Everolimus [27], in everyday clinical practice sorafenib and sunitinib are often used sequentially, despite their relevant similarities in terms of mechanism of action.

Available data suggest that there is no cross-resistance between sorafenib and sunitinib [18,28–32] or between sorafenib and bevacizumab [18,19,28], even though such

Table 5 Studies suggesting that sorafenib is efficacious after other VEGF-pathway-targeting agents

Segment	Trial	No. of patients	CBR (%)	PFS (months)
Post-sunitinib (total: 156 patients)	EU-ARCCS (EAP) [18]	69	52	4.1
	B. Rini (phase II) [28]	22	43[a]	4.4
	I. Imarisio (retrospective) [29]	18	50	6.0
	I. Tamaskar (retrospective) [30]	5	80	5.9
	A. Dham (retrospective) [31]	20	43	2.7
	M.P. Sablin (retrospective) [32]	22	63.6	3.9
Post-bevacizumab (total: 254 patients)	EU-ARCCS (EAP) [18]	42	72	5.0
	US-ARCCS (EAP) [19]	197	81	NA
	B. Rini [28]	15	43[a]	3.7

ARCCS, advanced renal cell carcinoma sorafenib; CBR, clinical benefit rate; EAP, expanded access programs; EU, European Union.
[a]Not available separately for prior sunitinib and bevacizumab.

evidence comes mainly from retrospective, nonrandomized (and therefore highly biased) series, as shown in (Table 5) [18,19,28–32].

Future developments

The excellent tolerability profile of sorafenib suggests that it could be combined with a number of other antitumor agents, either traditional chemotherapeutic agents or other molecularly targeted agents [33].

Furthermore, available evidence from a number of human xenograft models suggests that the antitumor activity of a number of anticancer agents could be enhanced by the concomitant administration of sorafenib [33]; indeed, several of these combinations have been exploited to design experimental studies in a variety of solid tumors.

Regarding RCC, so far sorafenib has been evaluated mainly within phase I and II studies (specifically aimed at targeting RCC or not), in combination with immune-stimulating drugs such as interferon [34–38] and IL-21 [39] (whereas studies in combination with IL-2 are ongoing); molecularly targeted agents such as bevacizumab [40,41], everolimus [42,43], bortezomib [44], temsirolimus [45], and perifosine [46]; traditional chemotherapeutic agents such as gemcitabine [47] or a combination of gemcitabine and capecitabine [48]; as well as with the anti-heat shock protein-90 geldanamycin [49].

So far, the more thoroughly studied combination is that with interferon, but from a theoretical viewpoint the most interesting are those with bevacizumab, everolimus and the PI3K/Akt inhibitor perifosine. In respect to the combination with bevacizumab, however, despite the high antitumor activity observed so far, available preliminary data suggest a significant increase in adverse events, preventing the safe administration of the two drugs at full doses [32].

Another promising strategy is that proposed by Amato *et al.* [50] (also tested in the second part of the already-mentioned first-line, phase II study vs. interferon [23]), that is, sorafenib's dose escalation; preliminary data suggest that sorafenib could be safely escalated up to 1600 mg per day, with promising antitumor activity, as demonstrated by a 32% objective response rate, and by a prolonged PFS ≥ 3 months for an additional 50% of patients.

Conclusion

Sorafenib is one of the four new molecularly targeted agents that have reached (or are going to reach) the bedside in the once-orphan field of the medical treatment of kidney cancer, and that have radically changed the natural history of this disease.

At present, it is the treatment of choice for patients refractory to cytokines, and as such, it has received a grade A recommendation by the European Urology Association guidelines [51].

As far as its use upfront, the above mentioned results of the first-line, randomized phase II study (although highly controversial) do not support its routine use in this setting; however, based on clinical judgement [52], sorafenib could be considered a first-line treatment option in specific subgroups of patients (e.g. in elderly patients [53,54]), mainly because of its favorable toxicity profile.

Further studies are nevertheless required to better define its activity in first-line, in patients who have failed other molecularly targeted agents [55], as well as in combination.

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