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# Protein kinase inhibitors in the treatment of renal cell carcinoma: sorafenib

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Sorafenib is an orally available multikinase inhibitor active on vascular endothelial growth factor receptor-2 and -3, platelet-derived growth factor receptor-β, B-RAF, C-RAF, flt3 and C-Kit. Phase I studies showed its activity on renal cell carcinoma (RCC) and other neoplasms and identified the schedule of 400 mg (two tablets) b.i.d. as better tolerated and potentially active. The original design selected for the principal phase II trial, randomization discontinuation trial, showed the particular activity profile of this drug: low objective response rates but significant increases in progression-free survival [PFS, which frequently translate in increased overall survival (OS)]. A pattern of response completely agrees with an antiangiogenic (cytostatic) agent. The potential efficacy of sorafenib was confirmed in immunotherapy-refractory advanced RCC cases by 'TARGETs', the largest randomized double-blind study ever carried out in kidney cancer. With a doubled PFS, a trend in OS and a modest toxicity profile, mainly grade 1–2 skin toxicity and diarrhea, sorafenib has been recently approved from the Food and Drug Administration and European Agency for the Evaluation of Medicinal Products for the second-line treatment of advanced RCC. Numerous trials are ongoing to test new schedules and drug combinations, while promising results were recently achieved also in hepatocellular carcinoma. With drugs such as sorafenib, angiogenesis could become an Achilles's heel for RCC.

**Key words:** angiogenesis, BAY 43-9006, protein kinase inhibitors, renal cell carcinoma, sorafenib, VEGF



## introduction

Renal cell carcinoma (RCC), which accounts for ∼3% of cancer incidence, is being detected with increasing frequency worldwide. Because of the large incidence of incidentally detected cases, the majority of RCC cases are actually diagnosed when still confined to the kidney and consequently managed with conservative or radical nephrectomy [1]. Unfortunately, however, one-third of these patients will experience a recurrence: with a median survival of ∼13 months and a 5-year survival rate of <10%, advanced kidney cancer has to be considered a lethal disease [2]. Prognosis of advanced RCC patients can be better defined according to the recently published prognostic classifications, which identify three risk categories (high, intermediate and poor risk). Median reported survival was 20 months for patients with any risk factors, 10 months for cases with one or two risk factors and only 4 months for those with three or more risk factors [3, 4].

RCC is notoriously considered a chemotherapy- and radiotherapy-resistant disease [2, 5]; as a consequence, the outcome of medical treatment with cytotoxic agents or immunotherapy for advanced disease has been, up to a recent past, rather disappointing. Cytokine therapy with interleukin-2 (IL-2) or interferon-α (IFN-α) was generally ineffective, and only few patients (∼4%) with advanced disease and excellent physical conditions have sometimes benefited from treatment with high-dose i.v. bolus IL-2, a very toxic regimen [6–11]. There are some suggestions that combination regimens with IL-2 and IFN-α, with or without 5-fluorouracil, are more active than monotherapy but with any significant impact on overall survival (OS) [12, 13].

The recently introduced molecularly targeted agents have disclosed new and promising perspectives for the treatment of RCC: an orphan disease considered, from both a biological and a ethical point of view, as an 'ideal *in vivo* model' to test new antiangiogenic molecules because of the strong dependency of both the hereditary and the sporadic forms of clear RCC from defects of the von Hippel–Lindau (VHL) gene. VHL inactivation, in fact, leads to an activation of the hypoxia factor pathway which causes a sustained release of vascular endothelial growth factor (VEGF), one of the most potent angiogenic factors, and a consequent strong tumor angiogenesis [14].

The continuous improvement in understanding molecular cancer biology has made possible to develop compounds able to target particular pathways activated only in cancer cells, including those regulating growth, survival and angiogenesis (targeted therapy). Among the variety of intracellular signaling pathways, activation of the protein kinase system, including tyrosine kinases (further subdivided into proteins with an extracellular ligand-binding domain and enzymes confined to cytoplasm and/or nuclear cellular compartment) and serin/threonine kinases, is one of the most frequently observed events

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[15, 16]. The abnormal activation of these kinases, target of sorafenib inhibitory activity, has been largely demonstrated in most human neoplasms [17].

## sorafenib

Among the recently introduced novel agents that target steps along the signal transduction pathway, sorafenib (Nexavar®, Bayer/Onyx) is the first oral multikinase inhibitor that targets upstream receptor tyrosine kinases (RTKs) as well as downstream serin/threonine kinases in both tumoral cell and tumor vasculature. Preclinical *in vitro* and *in vivo* experiments have indicated that sorafenib is a potent inhibitor of the C-RAF and B-RAF kinases, as well as the RTKs VEGF receptor-2 (VEGFR-2) and platelet-derived growth factor receptor-β [18]. The inhibition of these kinases results in the inhibition of cancer cell proliferation and angiogenesis, thus leading to an inhibition of tumor growth: multi-targeted approach represents an important tool available to oncologists for the treatment of advanced RCC.

## phase I clinical trials

Sorafenib was evaluated in various single-agent phase I studies at 50, 100, 200, 300, 400, 600 and 800 mg continuous or intermittent dosing, all administered by oral route, to a total of 197 patients with different advanced refractory solid tumors [19–21]. Drug safety was assessed by documentation and analysis of adverse events, laboratory testing of renal, liver and hematologic function and Electrocardiogram (ECG) monitoring. All patients reported at least one adverse event of any grade mainly consisting of fatigue (45% of patients), diarrhea (43%), anorexia (42%) and nausea (31%); other drug-related toxic effects included hand–foot syndrome, pyrexia, pruritus, hypertension, pain and rash. The majority of these adverse events were reversible. Grades 3 and 4 adverse events were reported in 66% of patients and the most relevant were fatigue (11% of patients), diarrhea and skin toxicity. Phase I trial data indicated the 400-mg b.i.d. schedule as a well-tolerated dose. Increasing the dose from 400 mg b.i.d. caused a significant increase of grade 3–4 toxic effects with a significant increase in the number of patients requiring treatment discontinuation due to side-effects at the 600- and 800-mg b.i.d. dose (as compared with 400-mg b.i.d. dose). Similar considerations can be made for dose modifications and dose delays. Pharmacokinetic data indicated that for the same total daily dose, a b.i.d. dosing gave a much higher exposure of sorafenib than an o.d. dose. A proportional increase in drug exposure with an increasing dose of sorafenib up to 400 mg b.i.d. was observed, with only a 13% further increase in exposure going from 400 to 600 mg b.i.d. and no apparent increase in sorafenib area under the plasma concentration–time curve when the dose was increased from 600 mg b.i.d. to 800 mg b.i.d. Consequently, the 400-mg b.i.d. dose was deemed correct to move into phase II and III clinical development.

## phase II clinical trials

Randomization discontinuation trial [22], a phase II placebo-controlled, randomized discontinuation study in patients with advanced refractory solid tumors, including 202 RCC patients, was designed to determine whether continued treatment with sorafenib inhibited the growth tumor in patients displaying stable disease (SD) after an initial 12-week course of therapy. The rationale underlying this design is on the basis of the need of differentiating patients having slow tumor growth due to drug effects from those with naturally slow-growing tumors. It is common knowledge, in fact, that some tumors, such as RCC, naturally grow slowly in some patients, regardless of treatment.

### study design

All patients received oral sorafenib (400 mg b.i.d.) for 12 weeks; at the end of this induction phase, the antitumor response was assessed with modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria and patients were divided into three main groups: patients with progressive disease (discontinued from the study); patients who responded to sorafenib (at least 25% shrinkage of the target lesions) who continued sorafenib in an open-label phase and patients with SD (target lesions within 25% of the baseline measurement) who were randomized to continue sorafenib (400 mg b.i.d.) or receive placebo (discontinuation). The third group represents the true experimental arm of the study.

Primary end point of the study was PFS measured 12 weeks after randomization. Overall, the study enrolled 202 patients with advanced RCC (in a total of 501 cases with different tumor types), the majority previously treated with IL-2 or IFN-α.

### activity

Fifty-eight of the 202 enrolled patients with RCC progressed and were discontinued from the study, 79 achieved a tumor shrinkage of at least 25% and continued open-label sorafenib, while 65 patients with SD were randomized to either sorafenib or placebo. At 12 weeks after randomization, 50% (16/32) of the patients receiving sorafenib but only 18% (6/33) of placebo patients were progression-free ($P = 0.0077$). The median PFS was significantly longer in the sorafenib group (163 days) as compared with placebo group (41 days) ($P = 0.0001$). Similarly, the median time to disease progression was 163 days for sorafenib group versus 43 days for placebo ($P = 0.0002$). All the 202 RCC patients enrolled in the study were assessed for safety. Adverse events of any grade ascribed to sorafenib occurred in 197 cases (98%). The most common grade 3–4 adverse events attributed to sorafenib were hypertension (49 patients; 24%) and hand–foot skin reaction (27 patients; 13%). Some other phase II trials have evaluated sorafenib in different solid tumors, such as hepatocellular carcinoma and non-small-cell lung cancer [23], while other studies evaluating sorafenib in combination with other drugs, such as IFN-α, in RCC are ongoing [24, 25].

## phase III clinical trials

TARGETs, a randomized multicenter, double-blind placebo-controlled phase III study carried out in patients with advanced immunotherapy-refractory RCC in 117 centers scattered in 19

countries all over the world, represents the largest randomized study so far carried out in RCC [26].

### study design

Eligible patients were randomized to receive either oral sorafenib 400 mg or matching placebo b.i.d. For ethical reasons, because of the second-line positioning of the study and the presence of a placebo arm, cases with a Motzer's poor-risk category classification [27] were not considered eligible for the study. Primary end point of the study was OS; secondary objectives were assessment of PFS, overall response rate (according to RECIST), health-related quality of life (QoL) and overall disease control rate [i.e. complete response (CR) + partial response (PR) + SD lasting for at least 28 days]. From November 2003 to March 2005, 903 patients were enrolled in the study and received sorafenib (451 patients) or placebo (452 patients). All patients' characteristics were well balanced between treatment arms.

The positive preliminary results of the TARGETs study were presented at the 2005 annual American Society of Clinical Oncology Meeting (first planned interim analysis on the basis of an independent assessment ~769 patients randomized before January 2005. Median PFS in sorafenib-treated patients 5.5 months versus 2.8 months of placebo group, hazard ratio 0.44, $P < 0.001$, positive trend in OS +39%, nonsignificant according to O'Brien–Fleming stopping rules). Because of the doubled PFS observed in the sorafenib arm, Food and Drug Administration requested to modify the study design and provide, for ethical reasons, sorafenib also to placebo-treated patients; as a consequence, 212 of these cases crossed to open-label sorafenib after May 2005, a probable significant bias for the intention-to-treat survival evaluation. At the following interim analysis, 6 months later, preliminary OS data showed a value of 19.3 months in cases initially treated with sorafenib and an improvement in the placebo group (15.9 months in cases who underwent to crossover and 14.3 months in patients remained with placebo). These data support the hypothesis of a potential advantage of sorafenib also when utilized in a delayed fashion. Presently, no definitive data about OS are available.

From an activity point of view, 10% of patients treated with sorafenib experienced a CR or PR (2% in the evaluation from the independent committee) but overall 84% of the cases presented a tumor control (intended as the sum of CR and PR plus stationary disease) deriving from a tumoral mass shrinkage in about other 74% of the cases and lacking any actual relationship between the entity of tumor shrinkage and PFS or OS with sorafenib. Moreover, the achievement of a SD in terms of RECIST or World Health Organization criteria but in presence of a large internal tumoral mass necrosis due to sorafenib agrees with the rationale of antiangiogenic approaches and has been demonstrated with some of the new imaging techniques (doppler ultrasound, dynamic contrast-enhanced magnetic resonance imaging [DCE-MRI]) [23, 28].

Treatment was well tolerated, with dermatologic and gastrointestinal toxicity, hypertension and fatigue as the predominant, mainly grade 1–2, side-effects. Any significant hematological toxicity was reported, while QoL improved in sorafenib-treated patients.

## conclusions

Sorafenib is an oral multikinase inhibitor characterized by an activity profile, which completely agree with what awaited from an antiangiogenic (cytostatic) agent: low objective response rates but significant increases in PFS and possibly survival. The modest toxicity profile of sorafenib has moved the interest of clinicians to new, and potentially more effective, sorafenib-based drug combinations. Particularly, promising seems to be preliminary data deriving from sorafenib plus IFN-α2a regimens, but a large amount of innovative studies is approaching. Other studies are ongoing to further reduce the modest sorafenib-induced skin toxicity and its impact on patient's daily activity.

Even if definitive data from ongoing large randomized phase III studies are still awaited, antiangiogenic agents will probably become the new mainstay of treatment of advanced RCC. Some important questions, however, remain unanswered: which patients have to be treated and when?, how to select the best candidates for any of these dispendious treatments? and how early evaluate in the single patient the potential benefits of these new agents? More trials and probably new trial designs are absolutely needed to reach an optimal management of this dramatic but intriguing disease.

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