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A new patient-focused approach to the treatment of metastatic renal cell carcinoma: establishing customized treatment options

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Accepted for publication 21 July 2010

Randomized controlled trials (RCTs) show that six targeted agents – sorafenib, sunitinib, temsirolimus, everolimus, bevacizumab and pazopanib – improve outcome in advanced renal cell carcinoma (RCC). The populations enrolled in the pivotal phase III studies differed, and, to date, no head-to-head comparisons allow us to judge relative efficacy and tolerability. Populations recruited to RCTs under-represent certain patient subtypes, notably the elderly and those with comorbidities. Choosing the agent most appropriate in a specific case requires that we take into account the characteristics of the patient, the nature of their disease, and the history and aims of therapy. Data from expanded access programmes and clinical experience may be as relevant as the results of RCTs when making this difficult decision. To show how different sources of data can be integrated, we propose a schema that acknowledges nine patient-, disease-, and treatment-related factors relevant to clinical decision-making and provides an easily understood visual indication of the strength with which a particular agent can be recommended for use in specific subgroups of patients. As an example, we show how this tool shows the suitability of sorafenib in RCC subpopulations of differing age, prognosis, performance status, tumour burden and distribution, treatment history, and comorbidity. This patient-focused approach has broad application to other agents and tumour types.

What's known on the subject? and What does the study add?

- Six targeted agents – sorafenib, sunitinib, pazopanib, bevacizumab, temsirolimus and everolimus – have been approved for the treatment of advanced renal cell carcinoma (RCC) based on evidence from large randomized controlled trials (RCTs). However, no head-to-head trials have been conducted to evaluate the relative efficacy of these agents in this setting.
- Patient populations included in clinical trials do not accurately reflect the wider population of patients with RCC, as certain subgroups, such as the elderly or those with co-morbidities, are typically under-represented.
- The optimum choice of therapy should be based on patient characteristics, nature of disease, and history and aims of therapy; however, there is currently no clear guidance for physicians in this decision-making process.
- A patient-focussed schema has been developed that acknowledges nine different patient-, disease-, and treatment-related factors relevant to clinical decision-making, and provides a visual indication of the strength of evidence with which a particular agent can be recommended for use in specific subgroups.
- To demonstrate the applicability of this tool, a review of all available evidence (published articles, congress presentations and personal communications) for sorafenib in RCC was conducted by a panel of experts, findings from which showed that sorafenib can be recommended for use in various subgroups of differing age, prognosis, performance status, tumour burden and distribution, treatment history and co-morbidity.
- This patient-focussed approach has broad application and can be used to assess other agents and tumour types.

KEYWORDS

sorafenib, renal cell carcinoma, cytokines, angiogenesis inhibitors

INTRODUCTION

For many years, interferon and interleukin-2 (IL-2) were the only systemic agents with activity against locally advanced or metastatic renal cell cancer (mRCC). Although cytokine treatment in general, and in particular high-dose IL-2, has shown efficacy in some patients, it is not widely applicable because of its association with substantial toxicity [1–3]. Most patients – and certainly those at poor and intermediate risk according to Memorial Sloan-Kettering Cancer Center (MSKCC) criteria [4] – are unsuited to cytokines. In this context, the

advent of agents targeted at abnormal angiogenesis and growth factor signalling within tumour cells has been widely welcomed. Six agents have been approved for the treatment of mRCC; sorafenib (Nexavar®, Bayer Schering Pharma AG, Berlin, Germany), sunitinib (Sutent®, Pfizer Limited, Sandwich, Kent, UK) and pazopanib (Votrient®, GlaxoSmithKline, Brentford, Middlesex, UK) are oral, multi-targeted small-molecule inhibitors of a range of kinases, and are commonly referred to as tyrosine kinase inhibitors, although sorafenib also targets the serine-threonine kinase Raf; bevacizumab (Avastin®, Roche, Basel, Switzerland) is an anti-VEGF monoclonal antibody; temsirolimus (Torisel®, Wyeth Pharmaceuticals, NJ, USA) and everolimus (Afinitor®, Novartis, Basel, Switzerland) inhibit the mammalian target of rapamycin pathway, an important determinant of cell growth and proliferation frequently deregulated in RCC. These agents have the potential to significantly alter the prognosis of mRCC; the challenge facing physicians is how to use them optimally to maximize the overall benefit to the patient.

PHASE III DATA DO NOT ADEQUATELY SUPPORT ALL TREATMENT DECISIONS

All six agents mentioned above have shown efficacy and safety in phase III randomized controlled clinical trials (RCTs). Although the data from RCTs provide an essential component of the decision-making process, they are not in themselves sufficient to fully support treatment choices for all patients with mRCC. Making comparisons across the trials is inappropriate as they were undertaken in populations with different prognostic factors, treatment histories and exclusion criteria. For example, sorafenib was compared with placebo in patients unsuitable for or failing previous cytokine therapy [5], while sunitinib, bevacizumab plus interferon and temsirolimus were all assessed in patients not previously treated with systemic therapy [6,7], and everolimus was assessed in patients heavily pretreated with targeted agents. Pazopanib was assessed in treatment-naive and cytokine-pretreated patients (53.5%, $n = 155$ of 290; and 46.5%, $n = 135$ of 290; of the phase III study population, respectively [8]). Temsirolimus was assessed predominantly in patients with a poor MSKCC risk status, whereas the other agents were assessed predominantly in patients with good or intermediate risk status [5–11]. In the absence of head-to-head comparisons, it is difficult to judge the relative efficacy and tolerability of each agent.

Additionally, patients enrolled in pivotal studies are often not typical of the wider population with the disease [12]. For example, exclusion of common comorbidities is frequent, resulting in under-inclusion of the elderly even in trials with no upper age limit [13]. Therefore, it is not surprising that Djulbegovic *et al.* [14] found that only 24% of the 154 clinically important clinical decisions they investigated (across 14 tumour types) were supported by 'level 1 evidence'.

In these circumstances, other types of clinical evidence can provide crucial additional information to guide treatment choices. Where trials are sufficiently large, subgroup analyses provide an indication of efficacy and safety in particular patient types. Expanded Access Programmes (EAPs) have broader inclusion criteria and more closely reflect the heterogeneity of patients seen in a 'real world' setting. Retrospective and case studies can provide valuable information in emerging (e.g. patients failing targeted therapy) and minority (e.g. patients with brain metastases) patient subgroups. It is also helpful to be guided by clinical experience, which is more likely than clinical trials to reflect the utility of the treatments in everyday practice [12].

DEFINING A NEW PATIENT-FOCUSED TREATMENT APPROACH

Patients with mRCC represent a heterogeneous group and no one agent will provide optimal benefit to all patients. For these reasons, we concluded that an individualized approach to treatment selection was needed. Initially four of the authors met, in March 2008, to review available data on the treatment of mRCC with targeted agents and to discuss and classify those factors that may have an impact on the tolerability and efficacy of treatment. This data review, as described previously [15], resulted in the design of a 'patient-focused schema' bringing together nine factors grouped under three headings: disease characteristics, patient characteristics, and treatment history and aims. At a second meeting, held in April 2008, the structure of the schema was reviewed and amended in consultation with a panel of eight additional advisors (see Acknowledgements) (Fig. 1a).

To test the utility of the approach, using sorafenib as an example, this second panel of advisors specifically reviewed data available on the treatment of mRCC with sorafenib and assessed the suitability of this agent for use in the subgroups of patients identified in the schema. To reach a consensus, all the advisors were asked to vote on a 'strength of recommendation' for sorafenib in each patient group. The schema was colour-coded to reflect the results of the vote as shown in Fig. 1b. White areas indicate a low strength of recommendation, light blue indicates a medium strength of recommendation, and dark blue indicates strong strength of recommendation. Note that although, for the purpose of demonstration, we have considered sorafenib in mRCC, the methodology could equally well be applied to other agents and tumour types.

APPLYING THE PATIENT-FOCUSED APPROACH TO IDENTIFY PATIENTS WHO MAY DERIVE MOST BENEFIT FROM SORAFENIB

DATA SOURCES

Data on the efficacy and safety of sorafenib for the treatment of mRCC were collected from published articles, conference presentations and personal communications from the oncologists and urologists on the panel of advisors.

Approval of sorafenib, the first tyrosine kinase inhibitor licensed for the treatment of RCC, was based on the results of Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET), the largest phase III trial of a novel treatment for this disease [5–16]. Median progression-free survival (PFS) in patients unsuitable for or failing previous cytokine therapy was 5.5 months with sorafenib and 2.8 months with placebo. There was a clear trend towards longer overall survival (OS) in sorafenib-treated patients, despite the crossover of placebo patients to active treatment. A preplanned secondary analysis, censoring for crossover in the placebo group, showed a significant OS benefit for sorafenib compared with placebo (sorafenib, $n = 451$: OS 17.8 months; placebo, $n = 452$: OS 14.3 months; hazard ratio 0.78; 95% CI 0.62–0.97; $P = 0.0287$) [16]. The efficacy and safety of sorafenib were confirmed in EAPs conducted in Europe and North America. In the European study (EU-ARCCS), 1155 patients with progressive or

advanced disease who had failed a previous systemic therapy or who were not suited to cytokines received open label sorafenib until progression or intolerance [17]. The similar North American study (N.Am-ARCCS) involved 2504 patients, contributing a large amount of data in a range of patient types more representative of those seen in the clinic [18]. Subanalyses of these studies provide an indication of the efficacy and safety of sorafenib in several different patient groups. A number of retrospective studies and case studies add valuable information on treatment in less common patient types, such as patients on dialysis [19,20] and patients with brain metastases [21]. Sorafenib has also been studied in a phase II trial vs interferon in patients with untreated advanced RCC, which showed similar PFS between groups, greater rates of tumour size reduction in the sorafenib group, and clinical benefit of switching to sorafenib after progression on interferon [22].

SORAFENIB IN PATIENT SUBGROUPS DEFINED BY DISEASE CHARACTERISTICS

The factors considered within this group are MSKCC risk category (good, intermediate or poor prognosis) [23], number of metastatic sites (none or one, two or three, or four or more); sites of metastasis (nodes, liver, lung, bone, or brain); and histology (clear or non-clear cell).

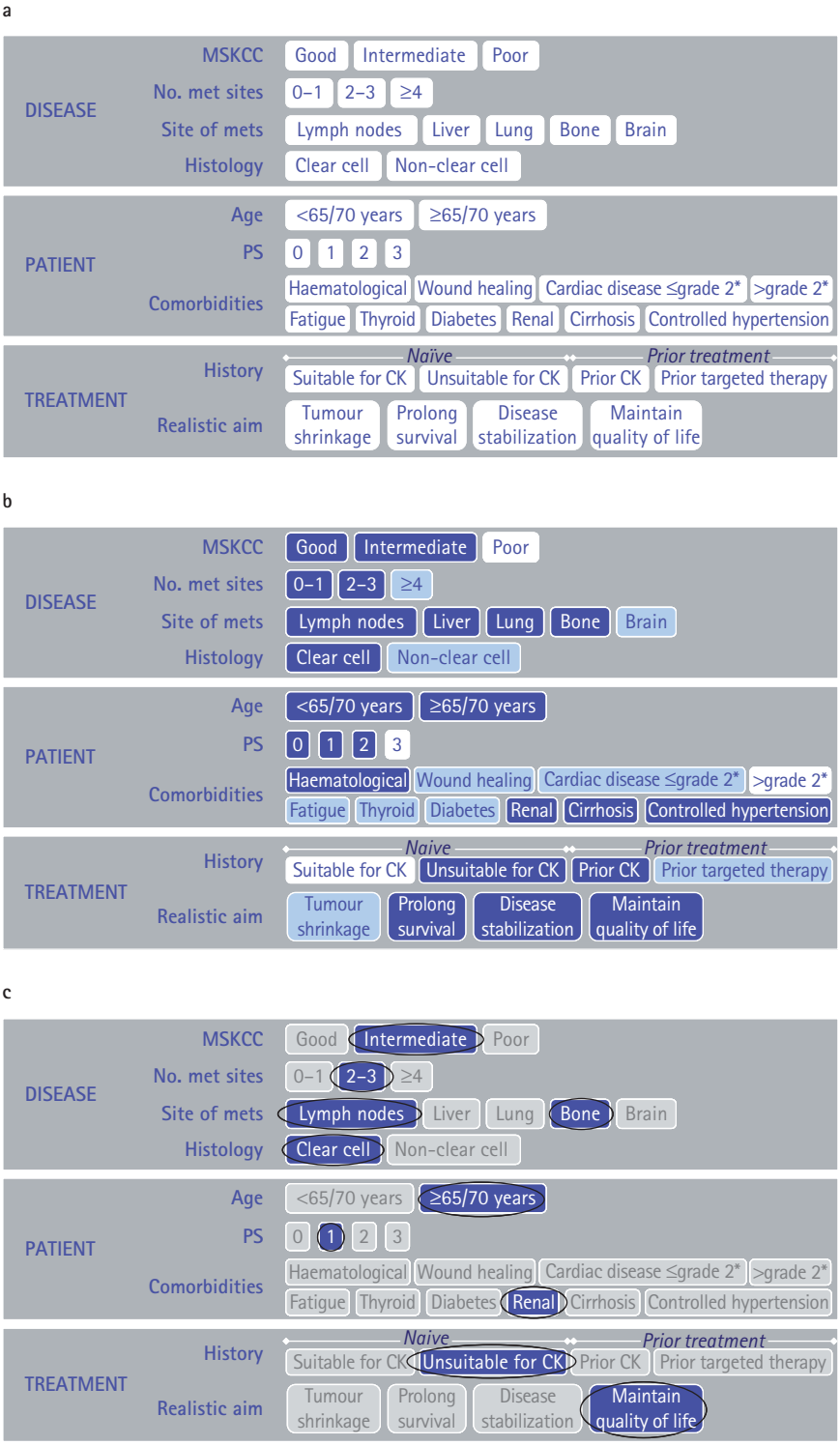
MSKCC risk category

Data from the TARGET trial showed that patients in the low MSKCC risk category (52% and 50% of patients randomized to receive sorafenib or placebo, respectively) and intermediate MSKCC risk category (48% and 49% of patients randomized to receive sorafenib or placebo, respectively), gained significant benefit from sorafenib, and the degree of benefit vs placebo was similar in both groups (Fig. 2) [5]. The study did not include high-risk cases and provided no guidance on use of sorafenib in this group.

Number and site of metastases

In a subgroup analysis of the TARGET study, hazard ratios for the reduced risk of disease progression on sorafenib were comparable between patients with liver or lung metastases, and the overall study population (Fig. 2) [5]. Furthermore, the median PFS on sorafenib was similar across these subgroups; 5.5 months for patients with lung metastases,

*FIG. 1. Proposed patient-focused schema: **(a)** characteristics to consider to individualize RCC treatment; **(b)** colour-coded schema indicating panel's consensus on the strength of their recommendation that sorafenib is suited to the various subpopulations of patient (low = white, medium = pale blue, or high = dark blue); **(c)** schema indicating factors to consider for a specific patient case (see text for details).*



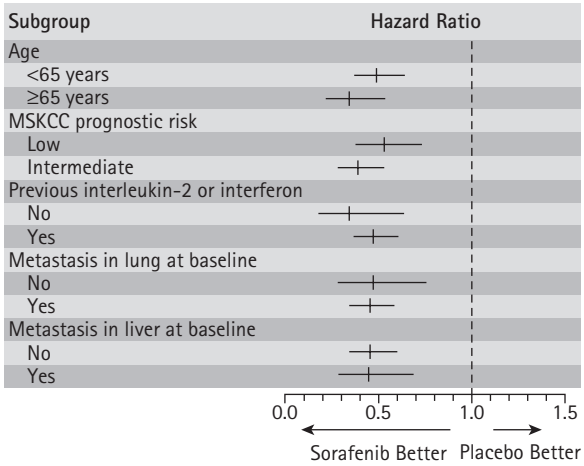


FIG. 2.
The benefit of sorafenib in different patient subgroups. Hazard ratios (with 95% confidence intervals) for progression-free survival (PFS) among subgroups of patients receiving continuous sorafenib, 400 mg twice daily, orally, compared with placebo. Adapted from Escudier et al. [5] with permission. Copyright © 2007 Massachusetts Medical Society. All rights reserved. MSKCC, Memorial Sloan-Kettering Cancer Center.

5.5 months for patients with liver metastases, 5.7 months for patients with bone metastases, and 6.1 month for patients with nodal involvement. Similarly, in the European EAP, the disease control rate (complete or partial response, or stable disease lasting 8 weeks or longer) among patients with metastases in two or more organs was 70.7% compared with 79.8% in patients with only one metastatic site [17,24]. The frequency of adverse events was similar in the two populations. These data underlie the consensus that sorafenib is effective and well tolerated in patients with up to three sites of metastasis, including those with bone metastases. There is less information about the role of sorafenib in patients with metastases in four or more different anatomic sites.

The EAPs also provide some indication of sorafenib efficacy in patients with pre-existing brain metastasis, a group generally excluded from clinical trials. Disease control was seen in 64% of 28 patients with controlled brain metastases in the European cohort [24] and 72% of 50 patients with brain metastases in the North American cohort [25]. In both studies there were no cases of cerebral haemorrhage in these patients [24,25]. It appears that adequately controlling hypertension is mandatory to prevent the risk of CNS bleeding [26,27]. These data are supported by a report of a 75-year-old woman who experienced a 95% reduction in brain metastases on treatment with sorafenib [21]. The small number of cases precludes any strong statement about safety and efficacy in patients with pre-existing lesions; however, it is interesting to note that retrospective analysis of data from a subset of patients in the TARGET trial showed that patients assigned to sorafenib were significantly less likely than placebo patients to develop brain metastases over 19 months of follow-up [28].

Histology

Traditionally, the 20% of RCCs with non-clear cell histology [29] have been thought to be resistant to systemic therapy. However, the EAPs provide evidence that the efficacy of sorafenib extends to non-clear cell tumours. In the European study, disease control was reported in 66% of 104 patients with papillary tumours, 67% of 46 patients with tumours with sarcomatoid features, and 61% of 103 patients with other non-clear cell histologies [17,30]. These figures are close to the 73% rate of disease control for the cohort as a whole. In the North American study, disease control was achieved in 84% of patients with papillary tumours, compared with 84% in the complete cohort [18].

Additionally, Choueiri and colleagues [31] retrospectively looked at 53 patients with either papillary or chromophobe RCC who had been treated with sorafenib or sunitinib. Although clinical responses were infrequent, both tyrosine kinase inhibitors appeared able to achieve disease stabilization. Evidence of clinical benefit with sorafenib has also been reported in a small Cleveland Clinic series of patients with RCC with sarcomatoid features [32].

SUBGROUPS DEFINED BY PATIENT CHARACTERISTICS

Age

Around 50% of patients presenting with RCC are aged 65 years or over, and a quarter are 75 years or older [33]. Comorbidities are more frequent in elderly patients, tolerability is perceived as a greater issue, and outcomes are thought to be worse [34,35]. In vulnerable patients, adverse events such as diarrhoea or stomatitis are of concern even when low-grade. However, there is also a determination that old age should not preclude access to effective treatment [34].

Evidence from RCTs shows that sorafenib reduces the risk of disease progression, compared with placebo, to the same extent in patients aged 70 years and over as in younger patients (Fig. 2) [36]. The disease control rate with sorafenib was 84% in both elderly and non-elderly patients [36]. The EAPs confirm that disease control with sorafenib is independent of age [18,37]. Importantly, sorafenib is also well tolerated in elderly patients. In the TARGET study, except for fatigue, the incidence of treatment-related adverse events in patients aged 70 years and over was similar to that in younger patients [36]. The European EAP provides similar reassurance [37]. Data from TARGET also show a beneficial effect of sorafenib on health-related quality of life in both older and younger patients [35]. Given this large body of data, there was unanimity among advisors that sorafenib can be used with a high degree of justification in patients of all ages.

Performance status

The TARGET study provides strong evidence that sorafenib benefits patients with Eastern Cooperative Oncology Group performance status of 0–1 [5]. The EAPs have included a wider range of patients and suggest that this benefit extends to patients with a performance status of 2. In the European cohort, although the proportion of patients with a performance status of 2 achieving disease control was less than in the performance status 0 and 1 categories, more than half of the patients obtained clinical benefit from sorafenib.

Comorbidities

Many patients with RCC have significant cardiovascular disease, diabetes and renal or hepatic dysfunction. Symptoms caused by comorbidities, such as fatigue, may be exacerbated by RCC treatments; and drug interactions with ongoing therapies can cause additional toxicities.

Cardiovascular Hypertension, obesity and cigarette smoking are risk factors for both cardiac disease and RCC, and around 20% of patients with RCC present with hypertension. Hypertension (controlled or not) was not an exclusion criterion for the TARGET study and more than one-third of patients included had hypertension at baseline [36]. In this trial, treatment with sorafenib was associated with a 17% incidence of treatment-emergent hypertension (any grade), compared with 2% among placebo patients; grade 3–4 hypertension was observed in 4% of patients receiving sorafenib [5]. In the North American and European EAPs, grade 3–4 hypertension was seen in 5% and 4% of patients, respectively [17,18]. Among TARGET patients, less than 1% discontinued because of hypertension. Cardiac ischaemia or infarction occurred in 3% of patients in TARGET and in 0.9% in the European EAP [17]. The incidence of cardiovascular adverse events among patients with RCC treated with sorafenib is therefore consistently low.

A subgroup analysis of data from the European EAP also showed that the presence of baseline cardiovascular disease (defined as coronary heart disease, stroke, hypertension, or congestive heart failure) did not have any negative impact on the efficacy or safety of sorafenib [38].

A pooled pharmacovigilance analysis of sorafenib phase I, II and III clinical trial data from over 2000 patients representing more than 1200 patient-years with multiple different tumour types showed an incidence of chronic heart failure and myocardial infarction of less than 2% [39]. A more detailed evaluation of the cardiovascular safety profile of sorafenib was conducted in a prospective open-label phase I study involving 53 patients treated for advanced solid tumours or lymphomas [40]. There was no notable effect on left ventricular ejection fraction over four cycles of therapy.

Figure 1b shows the advisors' consensus that a strong recommendation can be made for the use of sorafenib in patients with controlled hypertension. There was some support for its suitability in patients with moderate cardiac disease, but uncertainty about its appropriateness in patients with severe cardiac comorbidity.

Renal and hepatic impairment Mild renal impairment is common in patients with RCC. A series of four phase I studies found that even severe impairment did not affect the pharmacokinetics of sorafenib and its metabolites, and no dose adjustment was required [41–45]. Retrospective analysis of 32 patients, 14 of whom had a creatinine clearance of 60 mL/min or less, found that sorafenib was as effective as in patients with less impaired renal function, but may be more likely to lead to hand–foot skin reaction or diarrhoea [46]. A more recent study suggests that some dose reduction may be required to limit toxicity in patients with a creatinine clearance <40 mL/min [47]. Experience is accumulating suggesting that sorafenib is effective and well tolerated in patients undergoing dialysis [19,20,48]. Hence, renal impairment does not contraindicate the use of sorafenib, and the advisors agreed on a high strength of recommendation for the appropriateness of sorafenib in this patient subgroup.

This was also thought to be the case for patients with cirrhosis. Although sorafenib is metabolized and cleared primarily by the liver, dose adjustment has not been found necessary in patients with RCC who have mild/moderate hepatic impairment [45], and there is growing experience of its well-tolerated use in patients with hepatocellular carcinoma with moderate liver dysfunction (Child–Pugh stage A and B) [49,50].

Other comorbidities Clinically significant abnormalities of thyroid function are uncommon in patients treated with sorafenib and while biochemical abnormalities have been reported in certain populations [51,52] there is no requirement for monitoring of thyroid function during sorafenib treatment [45]. Haematological adverse events are uncommon with sorafenib: in the TARGET trial, the rate of grade 3–4 anaemia was the same in the sorafenib and placebo groups (3%), and there were no cases of febrile neutropenia or grade 4 thrombocytopenia [5]. Bleeding (any grade) was more frequent with sorafenib than with placebo, but the incidence of serious haemorrhage was not. A pilot study investigating the feasibility of using sorafenib before nephrectomy has found no evidence of interference with surgical technique, no increased risk of complications (including bleeding) and no adverse effect on wound healing [53].

Sorafenib treatment does not lead to hyperglycaemia or hypoglycaemia [47], and experience suggests that, with careful management (especially of hand–foot skin reaction), sorafenib can safely be used in patients with diabetes (C. Porta, personal communication).

PREVIOUS TREATMENT AND AIM OF CURRENT INTERVENTION

Suitability for and previous treatment with cytokines

In the TARGET study, both cytokine-treated and non-cytokine-treated patients experienced benefit from sorafenib (Fig. 2) [5]. The hazard ratio for reduced risk of progression vs placebo was 0.54 in patients who had failed previous cytokine therapy and 0.48 in patients without such exposure. The tolerability of sorafenib was also independent of cytokine history. The European EAP included 281 patients unsuited to cytokines and 700 who had been pretreated with interferon and/or IL-2 [17]. The rates of disease control in the two groups were very similar (71% and 74%, respectively).

Consistent with its indication, advisors therefore strongly supported sorafenib as a suitable treatment option both in cytokine-pretreated patients and in those unsuited to cytokines (Fig. 1b). Reasons advanced for considering a patient unsuited to cytokines include low likelihood of response, clinically significant organ impairment, inability to tolerate the common adverse events, and frank contraindications such as brain metastases or liver dysfunction [54–59]. According to the Programme Etude Rein Cytokines (PERCY)-quattro study, patients unlikely to benefit from cytokines are those with metastatic renal cancers of intermediate prognosis [54].

Previous targeted therapy

The data available from small studies and EAPs suggest little or no cross-resistance between targeted agents, including the two tyrosine kinase inhibitors sorafenib and sunitinib. In several retrospective studies, sorafenib resulted in an additional period of PFS and occasional responses in patients who had failed with sunitinib (Table 1) [60–66]. In the North American EAP, sorafenib achieved disease control in 81% of 197 patients who had previously been treated with bevacizumab [67]. This was no different from the rate among patients with no previous

TABLE 1 Summary of studies investigating treatment with sorafenib after sunitinib

Study	Reference	Number of patients	Median PFS on sorafenib (months)
Tamaskar *et al.* (retrospective)	[62]	5	2.3–12.7
Richter *et al.* (retrospective)	[65]	5	8.9
Choueiri *et al.* (retrospective)	[63]	7	5.3
Dudek *et al.* (retrospective)	[61]	20	2.9
Sablin *et al.* (retrospective)	[60]	22	3.9
Porta *et al.* (retrospective)	[64]	87	4.2
Shepard *et al.* (phase II)	[66]	24	3.8
Beck *et al.* (EU-ARCCS; expanded access)	[17]	69	4.1
Total		239	

EU-ARCSS, European Advanced Renal Cell Carcinoma Sorafenib trial; PFS, progression-free survival.

exposure to the antibody. Disease control was also achieved with sorafenib after failure on sunitinib or bevacizumab in the European EAP [17,30]. These data were confirmed in a prospective study in 42 patients previously treated with bevacizumab ($n = 18$) or sunitinib ($n = 24$). Although only 2% of patients experienced a tumour response, 52% of the patients experienced clinical benefit on sorafenib [66].

Objectives of therapy

The possible aims of therapy, which widely vary from one patient to another, encompass tumour shrinkage, prolongation of survival, disease stabilization and maintenance of quality of life. The TARGET trial showed a clear trend towards longer OS in sorafenib-treated patients, despite the crossover of placebo patients to active treatment [16], and a significant prolongation of the period without deterioration in heath-related quality of life [68]. In a randomized phase II study, sorafenib maintained quality of life whereas interferon did not [22]. Targeted therapies in general have been commended for their ability to improve outcome while allowing patients to maintain daily activities [68]. Data cited above, both from controlled trials and from EAP, show consistently high levels of disease control among sorafenib-treated patients [5,17,18]. Sorafenib was therefore considered an appropriate choice of therapy when the aim in an individual patient was to stabilize disease, maintain quality of life, or prolong survival (Fig. 1b).

The appropriateness of documenting tumour shrinkage with targeted agents such as sorafenib, which may induce necrosis rather than reduction in mass, has been much debated [69]. It has also been argued that patients may benefit from a reduction in tumour size that does not count as tumour response by standard criteria [70]. With this in mind, the consensus was that giving sorafenib with the aim of achieving tumour shrinkage was less well-founded than its administration for the purposes of disease control, prolongation of OS and maintenance of quality of life.

OUTCOME: STRENGTH OF RECOMMENDATION FOR THE USE OF SORAFENIB IN PATIENT SUBGROUPS

Figure 1b presents the consensus arrived at as a result of an extensive review of the available data. The colour-coding provides an easily understood visual indication of the strength of the recommendation that sorafenib be used for a patient with specific characteristics. The advisors agreed that sorafenib is an appropriate treatment choice for a range of patients including the elderly, patients in a good or intermediate MSKCC risk category, patients with previous exposure to other systemic treatments, patients with multiple metastases (including bone and brain), and patients wishing to prolong their survival through disease stabilization and maintained quality of life [5,17]. The drug remains well tolerated in patients with common comorbidities, including renal and liver dysfunction, and rates of cardiovascular adverse events and thyroid dysfunction are consistently low in sorafenib studies.

With the advent of new trial data and broader clinical experience, the level of consensus may change for some patient groups and the schema will need to be updated. Note that the strength of recommendation given here is based only on review of available data on sorafenib and is not intended to be comparative. Given the lack of head-to-head data on the treatment of patients with RCC with different targeted agents, evaluation of suitability for use in patient subgroups should be carried out for each agent separately.

POTENTIAL UTILITY OF THE APPROACH IN CLINICAL PRACTICE

How might this patient-focused schema be applied to assess the suitability of sorafenib for a particular patient? Faced with so many different patient types during everyday practice, each presenting a different combination of characteristics, assessing the appropriate clinical evidence can be a complex task. This schema can facilitate that task by providing a quick visual indication of which factors are important to consider and of the strength of clinical evidence available to support the use of, in this case, sorafenib in each situation. Take, for example, the hypothetical case of a 75-year-old woman with clear-cell RCC and metastases of the lymph nodes and bone. The patient currently has an intermediate MSKCC risk score and a performance status of 1. She has recently been complaining of fatigue and has a haemoglobin level of 10.1 g/dL. Based on the clinical evaluation, the patient is unsuitable for cytokine therapy because of hypertension and cardiac disease. The main aim of treatment is to maintain quality of life. Highlighting these disease, patient and treatment characteristics on the colour-coded schema makes it easier to focus on the key characteristics of this patient that may influence her response to or tolerability of treatment. According to the consensus recommendation of our panel of oncologists and urologists, in addition to first-line agents such as sunitinib, pazopanib and bevacizumab plus interferon and based on patient profile and treatment indication, this patient could be eligible for sorafenib therapy (Fig. 1c).

DISCUSSION

Randomized controlled trials show that six targeted agents are effective in advanced RCC. Compared with the situation only a few years ago, this has been described as an 'embarrassment of riches' [71]. However, it is not likely that any one therapy will benefit all

patients. Treatment should be tailored to meet individual circumstances and needs, and achieving this is a considerable clinical challenge. Notably, published international guidelines for the treatment of RCC, such as the kidney cancer guidelines of the National Comprehensive Cancer Network [72] recognize the importance of an individualized approach to therapy and base their recommendations on broader criteria, emphasizing the value of clinical judgement and experience to support treatment decisions for individual patients. The need to assess all available evidence when making clinical decisions has also been emphasized by Sir Michael Rawlins, Chairman of the UK National Institute for Health and Clinical Excellence, who stated that 'hierarchies [of evidence] place RCTs on an undeserved pedestal' [12].

At present it does not seem that targeted agents will offer a complete cure for mRCC; however, with careful management, they may offer the potential to transform mRCC into a chronically treatable disease. Indeed, the median OS for patients with mRCC has increased from around 13 months in the immunotherapy era to around 22 months in more recent years [4,73,74]. Where the aim of treatment is to stabilize disease and/or prolong survival, it is important not only to assess to what extent the selected first-line therapy can achieve this, but also to think about potential subsequent treatment options. Planning the sequential use of targeted agents in advance may help to achieve optimal clinical benefit from a maximum number of available treatments. Accumulating retrospective data suggests that a longer overall PFS can be achieved using sorafenib before sunitinib rather than sunitinib before sorafenib [60,61,63]. This possibility is under investigation in a phase III study prospectively evaluating the efficacy and safety of sorafenib followed by sunitinib vs sunitinib followed by sorafenib in the treatment of advanced mRCC (the SWITCH study, clinicaltrials.gov NCT00732914).

Sorafenib is licensed in Europe for the treatment of patients with advanced RCC who have failed, or are unsuitable for, interferon or IL-2-based therapy. As many patients are unsuited to treatment with cytokines, an individualized approach to considering the use of sorafenib in treatment-naive patients is warranted. Indeed, this is effectively the approach adopted in the National Comprehensive Cancer Network guidelines, which recognize sorafenib as a first-line option for *selected patients* (our italics) [72]. The exercise described above, which draws on EAPs and clinical experience as well as RCTs, suggests that sorafenib is well suited to many of the patient subtypes seen in routine practice, including those not generally represented in pivotal studies.

The process that we have used here to evaluate the evidence for sorafenib in the treatment of RCC can be equally well applied to other targeted agents. The schema we present, while acknowledging the complexity of everyday clinical decision-making, provides an easily assimilated means of conveying the strength of recommendation for use of a given agent in specific subtypes of cancer patient. Integration of this patient-focused approach into clinical practice should facilitate the appropriate use of targeted therapies and assist in optimizing overall levels of care.

ACKNOWLEDGEMENTS

The authors take full responsibility for the content of the paper, but gratefully acknowledge the invaluable role of the following advisors who contributed to development of the consensus recommendations for sorafenib using the patient-focused strategy described: Joachim Beck, Jose Pablo Maroto, Xavier Garcia del Muro, Ahmad Awada, Bohuslav Melichar, Ziya Kirkali, Aristotelis Bamias and Manuela Schmidinger. The authors also thank Esther Race, with financial support from Bayer Schering Pharma, for her editorial assistance in consolidating authors' contributions and formatting the manuscript and bibliography for submission.

CONFLICT OF INTEREST

Joaquim Bellmunt is a paid consultant and advisor for Pfizer, Hoffman La Roche, Bayer Healthcare, and Wyeth; Tim Eisen is a trustee of Kidney Cancer UK and has received honoraria for speaking and/or consulting from Pfizer, AstraZeneca, Bayer Schering Pharma, Roche, and Wyeth, and funds for research from Bayer Schering Pharma and Pfizer and he holds shares in AstraZeneca; Cezary Szczylik has received fees for speaking and consulting from Pfizer, Bayer Schering Pharma, Roche, and Wyeth, and funds for research from Bayer Schering Pharma; Peter Mulders is a paid advisor for AstraZeneca, Bayer Schering Pharma, GlaxoSmithKline and Pfizer, and has consulting agreements with Antigenics, Genprobe and Wilex; Camillo Porta has received funds for research from Bayer Schering Pharma and Novartis Pharma, and is a paid consultant or speaker for Hoffman La Roche, Novartis Pharma, Pfizer, Bayer Schering Pharma, and Wyeth. Source of Funding: the authors received travel reimbursement and honoraria from Bayer Schering Pharma for attending roundtable meetings during the development of this manuscript.

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Abbreviations: **IL-2**, interleukin-2; **mRCC**, metastatic renal cell carcinoma; **MSKCC**, Memorial Sloan-Kettering Cancer Center; **RCT**, randomized controlled trial; **EAPs**, Expanded Access Programmes; **PFS**, progression-free survival; **OS**, overall survival.