Bevacizumab as a treatment option in advanced renal cell carcinoma: An analysis and interpretation of clinical trial data

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Introduction

The incidence of kidney cancer, which accounts for 3% of all adult malignancies, has been increasing in recent decades. 1 Renal cell carcinoma (RCC), which makes up the vast majority of these cases, has a variable natural history. Risk factors identified as predictive of short survival by Motzer (Memorial Sloan-Kettering Cancer Center [MSKCC] criteria) were low Karnofsky performance status (PS), high lactate dehydrogenase level, low serum hemoglobin, high corrected serum calcium level, and an absence of prior nephrectomy. 2 In that retrospective analysis, patients with three or more risk factors, classified as poor risk, had a 4-month median survival; those with one or two risk factors (intermediate risk) had a 10-month median survival; and those with no risk factors (favorable risk) had a 20-month median survival. More recently, however, a phase III study of first-line treatments for patients with metastatic RCC (mRCC) reported that the probability of 3-year survival in both arms exceeded 40%, highlighting the change in the natural history of this disease in the era of targeted therapy. 3

The availability of molecularly targeted agents has improved outcomes for patients with renal cell carcinoma (RCC), a disease long considered refractory to systemic therapy. The hypervascularity observed in RCC tumors, which is driven by the inactivation of the von Hippel–Lindau gene, provided a rationale for targeting angiogenesis, in particular vascular endothelial growth factor (VEGF). Bevacizumab, a potent and specific anti-VEGF monoclonal antibody, has demonstrated significant clinical benefits when used in combination with interferon-alpha (IFN-α) for the treatment of metastatic RCC in two randomized phase III trials. The use of bevacizumab with IFN-α received approval in Europe for the first-line treatment of patients with advanced or metastatic RCC, and more recently this combination was approved for use in patients with mRCC in the United States. Bevacizumab with IFN-α has also been recommended by the National Comprehensive Cancer Network for first-line therapy of relapsed or metastatic unresectable RCC with predominantly clear cell histology. Two phase II studies suggest that bevacizumab has single-agent activity, which is characterized by encouraging progression-free survival rates and evidence of tumor regressions in patients with advanced or metastatic RCC. Here we review these trials along with recent and ongoing studies that explore the combination of bevacizumab with other targeted agents, its optimal sequencing with tyrosine kinase inhibitors, and its combination with low-dose IFN-α. Collectively, these studies allow the role of bevacizumab-based therapy to be defined in the context of a new and evolving algorithm for the treatment of patients with advanced RCC.

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is associated with IL-2 has narrowed its application to highly selected patients who are treated at specialized centers.12,13 IFN-α has produced modest benefits in unsselected patients, but randomized clinical trials have revealed a small survival benefit with manageable toxicity when compared to non-IFN-α control arms.14,15 As it became the de facto standard of care worldwide, the use of IFN-α as the control arm for randomized trials with targeted therapies was supported by regulatory agencies.16 The results of these investigations have, in general, established the superiority of targeted agents in previously untreated patients, thereby narrowing the future use of IFN-α as a single agent in this setting. The mechanistic rationale that underlies the use of one such targeted agent, bevacizumab—the anti–vascular endothelial growth factor (VEGF) monoclonal antibody and the subject of this review—is outlined below.

Targeting VEGF in RCC

A compelling argument for specifically targeting VEGF in RCC can be made on the basis of the unique genetic component of this disease (Fig. 1). Patients with von Hippel–Lindau (VHL) disease, which is transmitted in an autosomal dominant manner, have an increased risk of developing a number of cancers, including clear cell RCC. In the 1980s, linkage analysis revealed that the VHL gene resides on chromosome 3p25, a region commonly deleted or altered in sporadic RCC.17 The VHL gene itself was isolated in 1993 and has been found to function as a tumor suppressor.18 Biallelic inactivation of this gene is observed in the majority of sporadic clear cell RCC tumors as a result of either mutation or hypermethylation.19 Its gene product, pVHL, binds the hydroxylated form of hypoxia-inducible factor alpha (HIF-α) ultimately leading to its destruction by the proteasome. In the absence of functional pVHL, HIF-α accumulates, causing transcriptional activation and subsequent overexpression of proteins such as VEGF, platelet-derived growth factor beta (PDGF-b), and transforming growth factor alpha (TGF-α).20

VEGF, an important proangiogenic factor, is overexpressed in the vast majority of RCC tumors,11,21 and its expression level correlates with tumor stage and prognosis.22 The gross anatomic features of so-called hypervascularity observed in most renal adenocarcinomas, their propensity for vascular invasion and intravascular growth in the renal vein and inferior vena cava, and the large size of the primary tumor relative to metastases lend phenotypic support to the genetic rationale of targeting VEGF-driven tumor vascularization in clear cell RCC.

Over the last decade, a number of VEGF-inhibiting strategies, including the use of tyrosine kinase inhibitors (TKIs) and of neutralizing antibodies, have been evaluated in RCC. Among the clinically available antiangiogenic agents, bevacizumab is unique in that it exclusively targets VEGF, conferring true target selectivity by inhibiting the interactions of this ligand with all of the receptors to which it binds.24 Clinical trials of bevacizumab therefore afford the clearest insights into the potential utility of selective VEGF inhibition in RCC. These trials are summarized below.

Clinical safety and efficacy results of bevacizumab in RCC

In 2003, Yang and colleagues reported results from a seminal randomized phase II study of bevacizumab in patients with clear cell mRCC.25 Key inclusion and exclusion criteria for this and other trials, along with efficacy data, are shown in Table 1. A total of 116 patients were randomized to one of three arms: placebo, bevacizumab 3 mg/kg q2w monotherapy, and bevacizumab 10 mg/kg q2w monotherapy. Accrual was halted when an interim analysis revealed a time to progression (TTP) benefit in those receiving high-dose bevacizumab. A significant prolongation in TTP, as defined by the World Health Organization (WHO), was observed in this group relative to the placebo group (HR, 2.55; p < 0.001), and a smaller TTP benefit of borderline significance was reported for those receiving low-dose bevacizumab (HR, 1.26; p = 0.053). Four of the 39 patients in the high-dose bevacizumab group achieved an objective response, all partial, as best outcome (response rate [RR] = 10.3%; 95% CI, 2.9–24.2%), with one of them maintaining a partial response (PR) over the entire 2-year treatment duration. No objective responses occurred in the low-dose bevacizumab or placebo groups.

Bevacizumab treatment was found to be extremely well tolerated, with the only grade ≥3 toxicities being hypertension and proteinuria, which were largely asymptomatic. The onset of hypertension was noted to be unpredictable, sometimes occurring...

Fig. 1. Under hypoxic conditions (top), HIF-1α, in association with HIF-1β, acts as a transcriptional activator of the proangiogenic proteins VEGF, PDGF, and TGF-α. In the presence of oxygen, however, (bottom) HIF-1α is hydroxylated at one or two specific proline residues. This enables binding to pVHL, which in turn leads to polyubiquitination and, ultimately, the destruction of HIF-1α by the proteasome complex. The absence of functional pVHL, therefore, leads to HIF-1α accumulation and increased angiogenesis. Abbreviations: HIF-1α, hypoxia-inducible factor alpha; PDGF, platelet-derived growth factor; TGF-α, transforming growth factor alpha; pVHL, von Hippel–Lindau tumor suppressor protein; VEGF, vascular endothelial growth factor.
suddenly in patients who were months into treatment.³⁰ No life-threatening adverse events (AEs) potentially related to bevacizumab were observed in this study, which served as proof of principle for the utility of direct inhibition of VEGF in clear cell mRCC.

Further data regarding the single-agent use of bevacizumab in mRCC came from the control arm of a randomized phase II trial comparing bevacizumab (10 mg/kg q2w) plus placebo with the combination of bevacizumab (10 mg/kg q2w) and erlotinib (150 mg qd), a TKI targeting the epidermal growth factor receptor (EGFR).²⁶ A total of 104 patients, all classified as either low or intermediate risk by Memorial Sloan-Kettering Cancer Center (MSKCC) criteria, were enrolled. Both treatment arms demonstrated an impressive median progression-free survival (PFS) (8.5 months for the bevacizumab-alone arm and 9.9 months for the bevacizumab-plus-erlotinib arm, p = 0.58), although the objective response rates (ORRs), as measured by RECIST, were relatively low (13% and 14%, respectively; p = 0.999). Both regimens were well tolerated, but one death due to gastrointestinal perforation occurred in the bevacizumab-plus-erlotinib arm. AEs associated with TKIs (rash and diarrhea) were found only in the erlotinib arm, and similar rates of hypertension and proteinuria were observed in both arms. The authors concluded that although well tolerated, the addition of erlotinib to bevacizumab therapy did not provide clinical benefit compared with bevacizumab monotherapy, which had encouraging activity relative to historical controls.

Interestingly, individual measurements of tumor burden over time from both single-agent bevacizumab studies (Fig. 2)²⁶,³¹ suggest that the majority of patients treated with bevacizumab had tumor shrinkage; although, in most instances, the extent of tumor shrinkage did not meet the criteria for PR. These decreases in tumor burden were seen less frequently in the low-dose bevacizumab arm. Thus, on an individual basis, the effect of bevacizumab in patients with mRCC may be recognized by a subtle yet definitive decrease in tumor burden that allows for treatment individualization based on response. The efficacy data from these two single-agent studies would seem to contrast with results from trials of bevacizumab in other tumor types (non–small cell lung cancer, metastatic colorectal cancer, metastatic breast cancer), in which the clinical benefit with single-agent bevacizumab has been limited, even though combination use has proven efficacious.³² Given these results and the strong mechanistic rationale for anti-VEGF therapy in RCC, the single-agent utility of bevacizumab in mRCC remains an intriguing subject for further study.

Two randomized, multicenter phase III trials have now examined the combination of bevacizumab with IFN-α, the previous standard of care for systemic treatment of patients with mRCC. In both the industry-sponsored AVOREN study (N = 649) and the CALGB 90206 intergroup study (N = 732), patients with previously untreated mRCC were randomized to either bevacizumab (10 mg/kg q2w) plus IFN-α (9 MIU tiw) or IFN-α (9 MIU tiw).¹⁶,²⁸ The AVOREN study was placebo-controlled, whereas the CALGB 90206 study had an open-label design. In both studies, dose reductions for the management of drug-associated AEs were allowed for IFN-α but not for bevacizumab. The primary end point of both trials was overall survival (OS), and secondary end points included PFS, ORR, and safety.¹⁶,²⁸ Notably, as the AVOREN trial progressed, new agents, such as TKIs, became available to patients with progressive disease (PD), which may have confounded the interpretation of OS data. As a result, the study was blinded at the time of the final PFS analysis, and, on that basis, patients in the IFN-α arm who had not progressed were crossed over to the bevacizumab arm.

In the AVOREN study, the ORR was significantly higher in the bevacizumab arm (31.4% vs 12.8%; p = 0.0001), with 70% of patients in this group reporting tumor shrinkage compared with 39% of patients treated with IFN-α plus placebo. At a median follow-up of 22 months, the median PFS was significantly higher in the bevacizumab arm as well (10.4 months vs 5.5 months; HR = 0.57; 95% CI, 0.45–0.72; p < 0.0001), per independent review.²⁷ PFS benefit was demonstrated irrespective of age, tumor histology (clear cell or mixed), baseline VEGF level, or creatinine clearance.¹⁶ Retrospective analysis revealed that the PFS benefit was maintained in 39% of bevacizumab-treated patients receiving reduced-dose IFN-α (3 MIU or 6 MIU), for whom a substantial decrease in the rate of AEs followed dose reduction.³³ Risk stratification by MSKCC criteria demonstrated significant PFS ben-

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**Table 1**

<table>
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<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>ORR (%)</th>
<th>CR (n)</th>
<th>PR (n)</th>
<th>Response duration (months)</th>
<th>PFS (months)</th>
<th>p</th>
<th>OS (months)</th>
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<td>0</td>
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<td>7</td>
<td>6.7</td>
<td></td>
<td>8.5</td>
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<td>Bukowski et al.²⁵,²⁶</td>
<td>Bev 10 mg/kg q2w + Erl 150 mg qd</td>
<td>50</td>
<td>14.0</td>
<td>1</td>
<td>6</td>
<td>9.1</td>
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<td>9.9</td>
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<td>20</td>
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<td>5.5⁵</td>
<td>21.3⁵</td>
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<td>IFN-α 9 MIU tiw</td>
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<td>31.4</td>
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<td>92</td>
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<td>23.3³</td>
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<tr>
<td></td>
<td>IFN-α 9 MIU tiw + Bev 10 mg/kg q2w</td>
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<td>8.4⁴</td>
<td>&lt;0.0001</td>
<td>18.3⁵</td>
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</table>

Bev, bevacizumab; CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; Erl, erlotinib; IFN, interferon; mRCC, metastatic renal cell carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PS, performance status.

* No significant differences in survival between treatment groups were detected, although the study size was small.

Key inclusion criteria: mRCC with clear cell histology, ECOG PS 0 or 1, either prior IL-2 therapy or contraindication. Key exclusion criteria: history of CNS involvement.

Data from second interim evaluation.

Key inclusion criteria: mRCC with predominantly clear cell histology, prior nephrectomy, ECOG PS 0 or 1. Key exclusion criteria: prior systemic therapy, history of heart failure, angina, arrhythmia, myocardial infarction, stroke, brain, or CNS metastases.

Key inclusion criteria: mRCC with predominantly clear cell histology, prior nephrectomy, Karnofsky PS > 70%. Key exclusion criteria: prior systemic therapy, evidence of brain metastases, full-dose anticoagulation, significant cardiovascular disease.

Key inclusion criteria: mRCC with clear cell histologic component, Karnofsky PS > 70%. Key exclusion criteria: CNS metastases, heart failure, venous or arterial thrombosis, anticoagulation.


effect in the low- and intermediate-risk groups. However, the number of enrolled patients in the poor-risk category was small (8.3% of all enrolled patients), and, in this population, a significant PFS benefit was not detected, although the hazard ratio for progression was 0.81 (range, 0.46–1.42).26

Median OS values stratified by Motzer score and region for the bevacizumab combination arm compared with the IFN-α placebo arm were 23.3 months and 21.3 months, respectively (HR = 0.86; 95% CI, 0.72–1.04; \( p = 0.1291 \)), but the effects of crossover to the bevacizumab arm, as well as second-line therapies—which applied to 55% and 63% of patients in these arms, respectively—may have confounded the effect. Interestingly, median OS in patients receiving bevacizumab combined with reduced-dose IFN-α (26.0 months, \( n = 131 \)) exceeded median OS in the bevacizumab/IFN-α arm overall (23.3 months, \( n = 327 \)).27

In the CALGB 90206 study, the combination of bevacizumab with IFN-α was also associated with significant increases in median PFS (8.4 months vs 4.9 months; \( p < 0.0001 \)) and ORR (25.5% vs 13.1%; \( p < 0.0001 \)), relative to IFN-α alone. The hazard ratio for progression was 0.71 (95% CI, 0.6–0.8; \( p < 0.0001 \)).29 Thus, although the amount of PFS benefit conferred by the combination of bevacizumab and IFN-α differed slightly between AVOREN and CALGB 90206, the HRs for progression partly overlapped. Stratification by MSKCC risk factor revealed that median PFS values were 11.1 months vs 5.7 months in patients with no risk factors (26%), 8.4 months vs 5.3 months in patients with one or two risk factors (64%), and 3.3 months vs 2.6 months in patients with three or more risk factors (10%), for the bevacizumab combination and IFN-α monotherapy treatment groups, respectively. As in the AVOREN study, IFN-α dose reductions were undertaken in a large percentage of patients in each arm (64% and 47%, respectively).28

Median OS, the primary trial outcome, was 18.3 months compared with 17.4 months overall for patients in the bevacizumab combination and IFN-α monotherapy groups, respectively (unstratified log-rank \( p = 0.097 \)), and 32.5 months vs 33.5 months (\( p = 0.524 \)) for the MSKCC favorable-risk group (26% of patients), 17.7 months vs 16.1 months (\( p = 0.174 \)) for the intermediate-risk group (64% of patients), and 6.6 months vs 5.7 months (\( p = 0.25 \)) for the poor-risk group (10% of patients), respectively.29 Fifty-six percent of study patients proceeded to at least one subsequent systemic therapy, which may have affected these data. Those receiving second-line therapy had a median OS of 31.4 months vs 26.8 months (\( p = 0.079 \)) in the bevacizumab combination and IFN-α monotherapy groups, respectively. Among patients who did not, the values were 13.1 months vs 9.1 months (\( p = 0.059 \)), respectively. Thus, although both randomized multicenter phase III studies demonstrated a trend toward improved survival with the combination of bevacizumab and IFN-α relative to the latter alone, statistical significance was not observed in either, possibly because of the confounding effects of new second-line therapies upon disease progression.

In both studies, the most commonly reported grade 3–5 AEs in both arms were those known to be associated with IFN-α: fatigue and asthenia in AVOREN, and fatigue and neutropenia in CALGB 90206. Bevacizumab-associated AEs were less common and were those previously associated with bevacizumab in studies of other tumor types. Selected serious AEs reported in each arm of these trials, as well as those occurring in a phase III trial of sunitinib in RCC are summarized in Fig. 3 for comparison.30 New safety signals for bevacizumab were not detected in either phase III study.

Consideration of the significant PFS (Fig. 4) and ORR benefits demonstrated by the combination of bevacizumab with IFN-α therapy in both trials, along with the generally tolerable safety profile associated with the regimen, has resulted in a category 1 recommendation for the treatment of relapsed or metastatic unresectable RCC of predominantly clear cell histology.5 Evidence from the pivotal AVOREN trial resulted in approval by the European Medicines Agency (EMEA) for the combination of bevacizumab and IFN-α for first-line treatment of patients with advanced or metastatic RCC, and this combination regimen was also recently approved for the treatment of patients with mRCC by the US Food and Drug Administration (FDA) without specified limitations according to line of therapy.

End points for these studies deserve some brief comments. Both AVOREN and CALGB 90206 were designed to detect differences in OS, the gold standard of efficacy in oncology trials. However, in both studies, the availability and sequencing of additional targeted therapies may have impacted this primary end point, resulting in increased reliance on a secondary end point, namely PFS, which has previously been accepted as a surrogate end point for approval of some oncology drugs by the EMEA and FDA.35 Most investigators have taken this into account, designing subsequent trials with PFS as a primary outcome.

### Integrating bevacizumab into treatment guidelines

Targeted agents have brought about a change in the natural history of RCC. The anti-VEGF agent bevacizumab and other new drugs targeting angiogenesis through additional pathways (sunitinib,36 sorafenib,37 temsirolimus38) have considerably improved the outlook of patients with a disease once considered refractory to systemic therapy. In view of the number of options now available and the limited number of trials in which each drug has been used, a treatment algorithm based on clinical experience with these agents may prove useful.39,40 One such proposed algorithm is shown in Fig. 5. Evidence to date supports the use of bevacizumab plus IFN-α, or alternatively sunitinib, for the first-line treatment of patients with metastatic clear cell RCC who are categorized as

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Fig. 2. Changes in tumor burden over time in patients treated with (A) high-dose bevacizumab (10 mg/kg q2w), (B) low-dose bevacizumab (3 mg/kg q2w), and (C) placebo.30,31 Reprinted with permission from Wolters Kluwer Health.31
having either good or intermediate prognosis and who are not appropriate candidates for high-dose IL-2 therapy. Temsirolimus, an inhibitor of the mammalian target of rapamycin (mTOR), which induces cell cycle arrest and downregulation of a number of proteins, including VEGF, is recommended for poor-risk patients with previously untreated mRCC.

For patients initially treated with cytokine therapy, subsequent treatment with sorafenib or sunitinib has been shown to be effective. Given the success of targeted agents in RCC, however, an increasingly relevant question is: What is the optimal therapeutic strategy for treating patients progressing on antiangiogenic therapy in order to maximize efficacy and minimize toxicity over time? The order and timing of targeted therapies need to be balanced with their impact on patient quality of life. Sequencing of therapies has therefore become the focus of a number of studies. To date, several studies, both retrospective and prospective, have indicated that TKIs are active in patients with mRCC who have progressed.

Fig. 3. Selected grade 3 or greater adverse events reported in phase III trials of bevacizumab/interferon-α and sunitinib in renal cell carcinoma. Lilac bars represent sunitinib trial results, green bars represent trial arms in AVOREN, and blue bars represent trial arms in CALGB 90206. Abbreviations: Bev, bevacizumab; IFN, interferon-α; PBO, placebo; Sun, sunitinib. Bleeding events (hemoptysis and rupture of a preexisting abdominal aneurism) were responsible for two deaths in this treatment arm (N = 337). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 4. Kaplan–Meier progression-free survival. (A) AVOREN (investigator assessment). Reprinted with permission from Elsevier. (B) CALGB 90206. Reprinted with permission.
Given the multiple treatment options now available, patient comorbidities may increasingly be considered when making treatment decisions; drug-associated toxicities may impact the choice of agents; in particular, the choice between sunitinib and bevacizumab combined with IFN-α for first-line treatment.48 TKIs have been associated with painful hand-foot syndrome (HFS), which may significantly reduce quality of life for patients with pre-existing impaired mobility, and a study reporting an 8% rate of class III–IV congestive heart failure among 75 patients treated with sunitinib raises concerns about its use in patients with cardiac risk factors.49 Bevacizumab, on the other hand, is not subject to off-target effects that may be responsible for these toxicities50; however, it has been associated with other serious AEs that may limit its utility in certain patient subgroups, such as those with diverticular disease51 or a history of arterial thrombotic events.52

Ongoing studies and future possibilities

The combination of bevacizumab with IFN-α can also give rise to toxicities associated with the latter agent, such as fatigue, flu-like symptoms, and asthenia that may adversely affect quality of life. A retrospective analysis of patients in AVOREN who received reduced-dose IFN-α (3 MIU and 6 MIU) indicates that efficacy was maintained in this patient subset while the rates of these AEs were reduced considerably.53 A prospective study to confirm these findings in approximately 150 patients with mRCC who will be treated with bevacizumab (10 mg/kg q2w) and IFN-α (3 MIU tiw) has begun accrual in Europe (Table 2).54

Combining bevacizumab with other agents is the subject of a number of trials. A phase II single-arm study of bevacizumab (15 mg/kg q3w), IFN-α (3–18 MIU tiw), and vinblastine (0.1 mg/kg q3w) has begun recruiting patients.54 Combinations of bevacizumab with other targeted agents may display improved efficacy through blockade of the angiogenic pathways at multiple points. As previously noted, cross-resistance may not be complete, and the safety profiles of bevacizumab and TKIs appear to be largely orthogonal. Clinical reality, however, has introduced a cautionary note. A phase I trial of bevacizumab (10 mg/kg q2w) combined with sunitinib (25–50 mg qd) for patients with mRCC found that although efficacy was noted, the regimen was poorly tolerated, with a high proportion of patients experiencing grades 3 and 4 toxicities, including two cases of grade 3 microangiopathic hemolytic anemia, that required dose reductions or study discontinuation.55 Similarly, tolerability problems have been noted for the combination of bevacizumab with sorafenib in patients with solid tumors.56 Furthermore, improvements in efficacy resulting from such combinations are by no means assured.57

Combining bevacizumab with mTOR inhibition is also of interest and appears promising based on preliminary data.58 Additional studies of first-line treatment of patients with mRCC with the combination of bevacizumab and the oral mTOR inhibitor everolimus are ongoing.59 A randomized phase III study of the combination of bevacizumab with temsirolimus compared with bevacizumab with IFN-α for the first-line treatment of patients with advanced RCC is also underway.60 In addition, a phase II Eastern Cooperative Oncology Group (ECOG) trial, BeST, randomizes patients with mRCC of predominantly clear cell histology who have not been treated with antiangiogenic therapy into four arms: bevacizumab monotherapy, bevacizumab plus temsirolimus, bevacizumab plus sorafenib, and temsirolimus plus sorafenib.57 Final data collection is expected in 2012.

It is conceivable that bevacizumab monotherapy could provide a safety advantage over its combination with IFN-α and over TKI monotherapy. The bevacizumab-only arm of BeST should also provide additional data in this regard, although the trial includes no single-agent TKI arm that would allow for a direct comparison of

![Proposed algorithm for first-line treatment of patients with metastatic RCC](image1)

![Proposed algorithm for subsequent-line treatment of patients with metastatic RCC](image2)
the two monotherapies. It is expected that further randomized trials will be needed to confirm the results of this phase II, hypothesis-generating trial in any case.

Neoadjuvant antiangiogenic treatment of patients with mRCC has generated interest in part because of its potential for improved tolerability. Bevacizumab, either alone or in combination with erlotinib, was recently investigated in a single-arm phase II trial. Clinical outcomes were found to be comparable to postsurgical antiangiogenic therapy, although an increased incidence of wound-healing delays relative to historical controls was noted. The authors concluded that planned and ongoing phase III trials should clarify the role of presurgical antiangiogenesis in the treatment of RCC.

Conclusions

Bevacizumab, which has proven to be well tolerated and efficacious in a number of tumor types when combined with cytotoxic chemotherapy, has recently demonstrated significant clinical benefits in patients with mRCC when combined with IFN-α. In two large, randomized phase III studies, AVOREN and CALGB 90206, PFS (10.4 months vs 5.5 months in AVOREN, 8.4 months vs 4.9 months in CALGB 90206) and ORR (31.4% vs 12.8% in AVOREN, 25.5% vs 13.1% in CALGB 90206) were significantly increased relative to IFN-α alone, which was the previous standard of care. Regulatory approval for use in combination with IFN-α for the first-line treatment of advanced or metastatic RCC has been granted in Europe, and, more recently, the combination was approved for use in patients with mRCC in the United States. Furthermore, National Comprehensive Cancer Center has given it a category 1 recommendation for first-line treatment of relapsed or stage IV unresectable RCC of predominant clear cell histology.

In contrast with results from some other tumor types, single-agent use of bevacizumab has demonstrated safety and activity in two phase II RCC studies, which may speak to the highly vascularized nature and importance of the VHL/HIF-1/VEGF axis in this disease. Although such single-agent use could conceivably represent the most specific and perhaps safest approach to targeting this important pathway, more definitive evidence is needed before any such conclusion can be drawn.

Full elucidation of the potential of bevacizumab in RCC will also require further studies. Areas of interest include its potential clinical benefit in the adjuvant setting, phase III studies to define its efficacy and safety when used in combination with other targeted agents, and optimal sequencing in relation to TKIs. Such studies should help shape future, improved utilization and optimize clinical benefits for this agent, which has already become an important part of the treatment armamentarium for patients with RCC.

Conflict of interest statements

Dr. McDermott was a consultant for Genentech, Novartis, Wyeth, Glaxo-Smith Kline, and Roche. He received honoraria from Genentech, Novartis, Glaxo-Smith Kline, and Roche; and received research support from Novartis.

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