Rationale for targeted therapies and potential role of pazopanib in advanced renal cell carcinoma

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Abstract: Advanced renal cell carcinoma (RCC) remains a challenging, major health problem. Recent advances in understanding the fundamental biology underlying one form of RCC, ie, clear cell (or conventional) RCC, have opened the door to a series of targeted agents, such as the tyrosine kinase inhibitors (TKIs), which have become the standard of care in managing advanced clear cell RCC. Among the newest of these agents to receive Food and Drug Administration approval in this disease is pazopanib. This review will summarize what is known about the fundamental biology that underlies clear cell RCC, the data surrounding the previously approved targeted agents for this disease, including not only the TKIs but also the mTOR inhibitors and the vascular endothelial growth factor-specific agent, bevacizumab, and the newest TKI, pazopanib. It will also explore the potential role for pazopanib relative to the other available agents and where it may fit into the armamentarium for treatment of advanced/metastatic RCC.

Keywords: pazopanib, targeted therapy, tyrosine kinase inhibitor, clear cell renal cell carcinoma

Introduction
With 57,760 newly diagnosed cases anticipated for 2009 and an estimated 12,980 deaths from renal cell carcinoma (RCC), this disease remains a significant public health issue. It is known that the incidence of RCC is steadily rising, but the reasons underlying this observation remain unknown. For those who present with clinically localized tumors, surgery remains the mainstay of therapy and will cure the majority of patients. However, at least one-third of patients will either present with advanced or metastatic disease or develop this after initial curative resection. For this group of patients the prognosis is considerably worse. It is now well established that RCC is relatively resistant to traditional cytotoxic chemotherapy. Therefore, for many years the mainstay of therapy was based on cytokine-mediated approaches using either interferon alpha (IFNα) and/or interleukin-2 (IL-2). The results with these agents were less than satisfactory because they produced objective response rates in the order of only 10%–20%, with long-term durable responses in less than 5% of cases, at least for high-dose IL-2. Within the last 5 years there have been substantial gains in the management of advanced RCC that offer both hope and a new set of challenges and questions. The mainstay of these approaches is grounded in a deeper understanding of the biology of RCC and the so-called “targeted therapies” designed to attack specific important aspects RCC pathobiology. Several basic approaches have been utilized, including a class of agents designed to block the action of tyrosine kinase.
The tyrosine kinase inhibitors (TKIs) can often block the activity of more than one kinase, including those that act as receptors for important ligands in RCC biology, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). This review will focus on the published results of one of these new targeted therapies for RCC, the second-generation TKI, pazopanib. The aim will be to review the biology pertinent to RCC and the targeted therapies, summarize the other agents in this general class, describe the data specific to pazopanib, and to explore where pazopanib fits in the global approach to advanced RCC, and what questions remain to be answered.

**Clear cell renal cell carcinoma: central role of VHL**

There are at least 5 histologic forms of RCC, but by far the most prevalent is the clear cell (or conventional) type (ccRCC), which accounts for 75% of cases. The second most common is papillary RCC, which has two subtypes (Type 1 and Type 2), both of which have biology distinct from ccRCC. Type 1 papillary RCC is believed to be due to aberrations of the c-Met proto-oncogene, while Type 2 papillary RCC is thought to be due to mutations or abnormalities of the gene for fumarate hydratase, an enzyme involved in the Krebs cycle. At this time there are no specific agents available to target these distinct pathways outside the context of a clinical trial, so this review focuses specifically on the molecular biology of ccRCC. The pathogenesis of ccRCC centers on aberrations in the von Hippel-Lindau (VHL) gene and its protein product. Under normal conditions, the VHL protein predominantly functions in the oxygen sensing machinery of the cell and the cellular response to hypoxia. VHL complexes with several other proteins in the cytoplasm of the cell, specifically elongin B, elongin C, cullin-2, and Rbx, as part of an E3 ligase complex. This regulatory complex operates by ubiquitinating proteins, thereby marking them for subsequent degradation by the proteosomal machinery of the cell.

Under normoxic conditions, a critical regulatory molecule, known as hypoxia-inducible factor alpha (HIF\(\alpha\)), is hydroxylated by a series of oxygen-sensitive prolyl-hydroxylases. Hydroxylation of these proline residues allows the E3 ligase complex to bind HIF\(\alpha\), predominantly through the protein VHL. The binding of VHL and the E3 ligase complex to HIF\(\alpha\) leads to the latter being ubiquitinated and marked for subsequent degradation. As a result, in the typical cellular environment, in which there are normal oxygen levels, the amount of HIF\(\alpha\) within the cell is maintained at a low level.

In contrast, under hypoxic conditions, HIF\(\alpha\) is not hydroxylated, and therefore fails to bind to VHL and the E3 ligase complex, so is not degraded (see Figure 1). The normal cellular response to hypoxia is therefore to raise HIF\(\alpha\) levels, allowing it to build up within the cytoplasm and bind with a similar molecule, HIF\(\beta\). This HIF\(\alpha/\beta\) heterocomplex then translocates to the nucleus and binds regions of nuclear DNA known as hypoxia response elements (HRE) within the promoters of genes important in the cellular response to hypoxia. Binding of the HIF\(\alpha/\beta\) complex to HRE in the promoter region, in turn, transcriptionally upregulates mRNA and subsequent protein levels. The critical HIF-regulated genes include VEGF, PDGF, transforming growth factor alpha (TGF\(\alpha\)), carbonic anhydrase IX, erythropoietin, glucose transporter, and others.

When there is an abnormality or mutation in the VHL protein such that it either cannot function or its levels are abnormally low or absent in the cell, HIF\(\alpha\) cannot be bound to the E3 ligase irrespective of the oxygen levels in the cell, and so is constitutively present at high levels (see Figure 1). Constitutively high cellular levels of HIF\(\alpha\) in turn lead to ongoing interaction of HIF\(\alpha/\beta\) complexes with HRE in the nucleus and the genes normally regulated by HIF, such as VEGF, PDGF, and TGF\(\alpha\), will be abnormally activated, leading to the development of ccRCC.

**Vascular endothelial growth factor and its receptor**

Although HIF\(\alpha\) regulates a number of genes, the one which has been the focus of most research and drug development has been that for VEGF which plays a central role in angiogenesis, ie, the process of making new blood vessels, including those generated by tumors as they grow. It is now recognized that this process of tumor-induced angiogenesis is critical to malignant tumor progression across a variety of tumors. Clinically it has also been long appreciated that ccRCCs in particular are generally hypervascular tumors. The family of VEGF proteins includes several subtypes, ie, VEGF-A, -B, -C, -D, -E, and placenta growth factor-1. These protein ligands in turn exert their action by binding to one or more receptors specific for VEGF at the cell surface, VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flik-1), and VEGFR-3 (Flt-4). Among these receptors, it is generally felt that VEGFR-1 and -2 are more important for angiogenesis, whereas VEGFR-3 is more important for lymphangiogenesis. Pazopanib was initially discovered as part of a drug screen for molecules that would block the action of VEGFR-2.
All members of the VEGF receptor family are cell membrane-associated tyrosine kinases. When VEGF (the ligand) binds to its receptor (VEGFR), it induces a conformational change in the receptor that switches on its tyrosine kinase activity. This kinase activity phosphorylates key proteins in a series of signaling cascades that include a series of molecules that are often also tyrosine kinases themselves. Examples of these signaling cascades include the RAF-MEK-ERK series of kinases and the phosphatidylinositol-3 kinase-AKT-mTOR pathway. The activation of these pathways in turn is what leads to changes in endothelial cell activation, proliferation, migration, and cell survival.34-37,40 This complex interplay
between multiple pathways, including those from other HIF target genes, ultimately leads to carcinogenesis through a mechanism that has not been completely elucidated to this point.

The key therapeutic observations from this biology are that kinases are critical components at several levels in this process, so an agent such as pazopanib or the other TKIs, that are able to block tyrosine kinase activity may be able to inhibit this cascade at several levels, depending on the kinase specificity of the particular agent. Another important observation with therapeutic implications is that the mammalian target of rapamycin (mTOR), a potential downstream target of VEGF, also acts to increase the starting cellular levels of HIFα. Therefore, in theory, abnormal VHL function can set up a vicious cycle in which HIFα levels rise, leading to abnormally high VEGF levels, which bind to and abnormally increase VEGFR activity, which leads to abnormally high activation of the phosphatidylinositol-3 kinase-AKT pathway. While this has many potential downstream effects, one is to activate mTOR. This can then induce even higher levels of HIFα. In principle, this could lead to a vicious positive feedback loop exacerbating the defect started by abnormal VHL function.

**VHL-HIF-VEGF biology and targeted therapy**

Understanding the basic biology underlying ccRCC, in particular the central role played by the VHL-HIF-VEGF axis, is important because the various members of this cascade are the therapeutic targets for most of the agents currently used in the management of advanced ccRCC. The concept of targeting these specific signaling molecules is the fundamental underpinning of the so-called “targeted therapies”, which are now the standard of care in managing this disease. This principle has resulted in two fundamental, but interrelated, categories of targeted therapeutics, ie, those that block the mTOR pathway and those that block the VEGF pathway.

**Inhibitors of the mTOR pathway**

As already described, aberrations in VHL underlie carcinogenesis in ccRCC predominantly through the accumulation of HIFα. Therefore, one potential way to target ccRCC is to block those pathways which regulate the starting levels of HIFα. Of the many potential pathways that influence HIF expression, from a therapeutic standpoint the most important is the Akt/mTOR pathway. Due to the vicious positive feedback loop discussed previously, a number of agents that inhibit mTOR have been developed (rapamycin, temsirolimus, and everolimus). Of these, only temsirolimus and everolimus have Level 1 evidence supporting their use and are approved by the Food and Drug Administration (FDA) for the management of advanced RCC.

Temsirolimus is a water-soluble ester of sirolimus, an older agent. In a large-scale, prospective, randomized Phase III trial in which patients with high-risk metastatic RCC were randomized to receive intravenous temsirolimus alone, IFNα alone, or both agents, temsirolimus as monotherapy improved both progression-free survival and overall survival compared with either IFNα or the combination. As a result of this study, temsirolimus is generally the preferred front-line option in patients with high-risk metastatic ccRCC. It is also worth noting that in the Phase III temsirolimus trial, some patients with non-ccRCC were included in the study and temsirolimus showed activity in these patients as well. Therefore, temsirolimus is also often used in the setting of non-ccRCC, including in patients with advanced papillary RCC.

Because temsirolimus is generally used for metastatic RCC patients felt to be at high risk for a poor outcome, it is important to understand the criteria used to try and make that determination. Up until recently these patients have been stratified as having low-, intermediate-, or high-risk disease according to the so-called Motzer criteria. This system is based on a series of 5 potential high-risk features found to predict poor prognosis in patients with metastatic RCC treated with IFNα. These features include poor Karnofsky performance status, high lactate dehydrogenase, low serum hemoglobin, high corrected serum calcium, and time from RCC diagnosis to starting systemic therapy of less than 1 year. Patients with no high-risk features are considered low-risk, those with one or two features are intermediate-risk, and those with 3 or more features are considered high-risk. Studies are actively investigating how the advent of targeted newer therapies may have influenced or changed these criteria. The temsirolimus trial used these criteria with the addition of one additional high-risk feature, ie, the presence of multiple organ metastases.

More recently, the oral mTOR inhibitor, everolimus, has also been tested in a large-scale, prospective, randomized, placebo-controlled Phase III trial in patients who had failed prior targeted therapies, including TKIs. Patients in the everolimus arm had better progression-free survival compared with the placebo arm. As a consequence, everolimus is generally viewed as the standard second-line therapy in the setting of TKI failure.
Inhibitors of the VEGF pathway

Bevacizumab

Targeting the VEGF pathway has been accomplished utilizing two distinct approaches. The most direct and conceptually easiest way is to target the VEGF protein directly. A number of approaches have been explored to accomplish this, but the most advanced is the humanized monoclonal antibody to VEGF, bevacizumab (Avastin®, Genentech/Roche). This novel intravenous agent was tested in a Phase III trial in combination with IFNα versus IFNα alone for men with previously untreated advanced RCC. The combination regimen demonstrated improved progression-free survival compared with the IFNα alone arm (10.2 months versus 5.4 months, respectively). As a consequence, bevacizumab in combination with IFNα is now approved for use in advanced RCC.

Tyrosine kinase inhibitors

A second approach to blocking the VEGF pathway is to interrupt signaling from either the VEGF receptor or signaling downstream from the receptor, rather than blocking the molecule itself. As alluded to earlier, the receptors for several HIF targets, such as VEGF, PDGF, and TNFα are all tyrosine kinases. Furthermore, the downstream targets of these tyrosine kinase receptors are in turn often kinases in the RAF-MEK-ERK and the PI3-kinase-AKT-mTOR pathways. Molecules designed to target these kinases are referred to as TKIs. Early attempts to develop TKIs tended to focus on those agents which were relatively specific for the VEGF receptor itself. However, overall, the results were disappointing and the pursuit of these highly specific VEGFR agents has been largely abandoned. What has become apparent is that TKIs that are more “promiscuous”, ie, less specific and able to inhibit more than 1 kinase, seem to be more effective, presumably due to the inhibition of multiple pathways simultaneously. This concept has led to the development of several TKIs, including three currently approved for use in advanced RCC, ie, sunitinib, sorafenib, and the latest to be approved by the FDA, the second-generation TKI, pazopanib. In addition to these compounds, there is an ever-expanding list of potentially active agents in various stages of development (eg, AG-013736, PTK787, and ZK222584). However, for this review, we will focus on the three approved for use in metastatic RCC, with particular emphasis on pazopanib (more in-depth reviews of the other agents have already been published).

One of the first TKIs to be developed is the orally bioavailable, multitargeted TKI sunitinib (Sutent®, Pfizer). Developmental and preclinical studies have shown that sunitinib blocks the kinase activity of several important receptors, including VEGFR and PDGFR. Promising Phase I and Phase II studies in patients with advanced ccRCC led to a large-scale, prospective, randomized Phase III trial of 750 patients with advanced ccRCC who had not received prior systemic therapy (front-line setting). Patients in the sunitinib arm had a better median progression-free survival (11 months) compared with the IFNα arm (5 months). The objective partial response rate for the patients on sunitinib was 31% (compared with 6% for IFNα). Overall toxicity was manageable, with the most common Grade 3/4 adverse events being hypertension (8%), fatigue (7%), diarrhea (5%), hand–foot syndrome (5%), neutropenia (11%), lymphocytopenia (12%), and thrombocytopenia (8%). Sunitinib was approved for use on the basis of this study and has become the de facto standard front-line regimen for favorable-risk, advanced ccRCC.

A second, orally bioavailable, multitargeted TKI is sorafenib (Nexavar®, Onyx/Bayer). This was actually the first targeted therapy approved for use in advanced RCC in 2005, and was originally developed as an inhibitor of Raf-1, a protein kinase in the Raf/MEK/ERK pathway which lies downstream of receptors such as VEGFR and PDGFR. Later, it was found that sorafenib was also able to inhibit other tyrosine kinases, including VEGFR and PDGFR. The Phase II studies with sorafenib showed improvements in progression-free survival, which prompted a large-scale, multicenter, international, randomized, prospective trial of 903 patients with advanced ccRCC who had failed 1 or more prior systemic therapies (second-line therapy). Patients were randomized to receive oral sorafenib or placebo. Progression-free survival was significantly better in the sorafenib arm, and therapy was generally well tolerated, although there were rare cases of significant hypertension and cardiac ischemia. It should be noted, that objective partial responses were generally uncommon with sorafenib. Sorafenib is now also approved for use in advanced ccRCC, although its use has generally been restricted to the second-line setting.

Pazopanib: a second-generation tyrosine kinase inhibitor

N(4)-(2,3-dimethyl-2H-indazol-6-yl)-N(4)-methyl-N(2)-(4-methyl-3-sulfonamidophenyl)-2,4-pyrimidinediamine (pazopanib) was initially discovered as part of a drug screen for agents that would potently inhibit VEGFR-2. However,
it has also been shown that, like the other therapeutically relevant TKIs, such as sunitinib and sorafenib, pazopanib can block the kinase activity of VEGFR-1, VEGFR-3, PDGFrα, PDGFrβ, as well as c-Kit.39,63,64 Pazopanib has been shown in vitro to inhibit the proliferation of human umbilical vein endothelial cells with an IC\textsubscript{50} of 21 nM.39,64,65 Studies using a variety of in vivo human xenografts in mice have demonstrated that pazopanib may have activity against a wide variety of malignancies, including prostate, colon, lung, melanoma, breast, as well as RCC.64 The optimum steady-state concentration of pazopanib required to inhibit VEGFR-2 in vitro is much higher than the IC\textsubscript{50} of the in vitro studies, in the order of 40 μmol/L, which is thought to be due at least in part to the very high proportion of pazopanib which is protein-bound in vivo (over 99%).64,65 The elimination of pazopanib is thought to be mainly via metabolism through the cytochrome P450 system and in particular CYP3A4, although contributions are also made by CYP1A2 and CYP2C8.39,65,66

On the basis of these promising preclinical studies, further clinical development of pazopanib was undertaken.

**Clinical trial data for pazopanib**

The first published Phase I trial of pazopanib was initiated in patients with a variety of refractory solid tumors.67 On the basis of the preclinical data, this trial was designed to achieve a steady-state pazopanib concentration of 40 μmol/L. Sixty-three patients were enrolled, with 43 in the dose-escalation phase of the study and 20 in the dose-expansion phase. The oral dose of pazopanib was increased from 50 mg 3 times per week to 2000 mg once per day and 300–400 mg twice per day. The most common toxicities were hypertension, diarrhea, hair depigmentation, and nausea, with hypertension being the most frequent Grade 3 toxicity. Dose-limiting toxicities were experienced at 800 mg and 2000 mg daily, while steady-state exposure was noted at doses at or above 800 mg daily. The mean elimination half-life of pazopanib was found to be 31.1 hours, and the mean target trough concentration was achieved at 800 mg once per day. In the group as a whole, 3 patients had an objective partial response and a further 14 had stable disease for 6 months or longer. Based on this study, 800 mg once per day was chosen as the dose to move forward for further clinical study. Of interest, 10 patients had refractory metastatic RCC, of which 4 achieved stable disease and one had an objective partial response.64 All of these patients showed some “clinical benefit”, and were treated with doses of 800 mg or higher, whereas the five who showed no obvious drug response were all treated with lower doses and did not reach the target trough concentration of >40 μM.

The encouraging results of this Phase I trial prompted a series of Phase II trials in patients with multiple solid tumors, but this review remains focused on a trial done for advanced ccRCC.68 This trial was originally designed as a randomized discontinuation study, similar to earlier Phase II studies of sorafenib,23,61 but was later changed to a more traditional open-label Phase II study based on the interim review by the study’s data safety monitoring committee after the first 60 patients demonstrated a 38% objective/overall response rate at 12 weeks. In total, 225 patients were enrolled, of whom 69% were treatment-naive (front-line) while 31% had failed either cytokine therapy or a bevacizumab-based regimen. The objective/overall response rate was 35%, with a median progression-free survival of 1 year. The most common adverse events encountered were similar to those reported in the Phase I study, and included diarrhea, fatigue, hair depigmentation, and elevations of aspartate transaminase and alanine transaminase.

The promising results of this Phase II study in turn led to a large, prospective, randomized, double-blind, placebo-controlled, international Phase III trial of pazopanib in patients with locally advanced or metastatic RCC.69 Histology had to be either pure or predominant ccRCC, consistent with the majority of Phase III trials with the other approved TKIs. The trial was originally designed to enroll patients who had failed prior cytokine therapy. However, due to the success of other TKIs, the population of cytokine-refractory patients rapidly became quite small, and the study was therefore amended to also include treatment-naive patients. Patients were randomized 2:1 to pazopanib at 800 mg orally once daily or to placebo. Of the 435 patients enrolled, 233 (54%) were treatment-naive. Patients randomized to pazopanib had a longer median progression-free survival compared with patients randomized to placebo (9.2 versus 4.2 months, respectively, hazard ratio [HR] 0.46, 95% confidence interval [CI] 0.34–0.62; P < 0.0001). This was also true in both the treatment-naïve (11.1 versus 2.8 months) and prior cytokine-treated subgroups (7.4 versus 4.2 months). The overall objective response rate was 30%, with the vast majority being partial responses compared with 3% for patients on placebo (P < 0.001). Complete responses occurred in 1% of patients on pazopanib. The median duration of response was greater than one year. Toxicity was generally manageable, with the most common Grade 3/4 adverse events being diarrhea (3%), hypertension (4%), asthenia (3%), and alterations in alanine
transaminase (12%) or aspartate transaminase (7%). Notably, Grade 3/4 hematologic adverse events were relatively uncommon. There was no meaningful difference in quality of life in the pazopanib-treated patients relative to placebo. On the basis of this trial, pazopanib was approved for use in advanced/metastatic RCC by the FDA in October 2009.

**Pazopanib in context of other targeted therapies**
The therapeutic landscape for ccRCC has changed dramatically in the last 5 years. Less than a decade ago, the options were essentially two, ie, IFNα or high-dose IL-2. Neither was particularly satisfactory, and so the explosion of available options in many ways is a boon for both patients and their physicians. However, with this plethora of options come new questions and challenges. One of the first issues is the proper sequence and context in which the various new agents discussed in this review should be utilized. For the mTOR inhibitors, the Phase III data clearly support the use of temsirolimus as the first-line agent of choice for patients with intermediate- to high-risk metastatic disease. Similarly, the Phase III data for everolimus support its use in patients who have failed prior TKI therapy. Among the TKIs, however, the situation is not quite as clear.

In general, sorafenib is not typically used in the front-line setting and is usually utilized predominantly as a second-line agent. However, for the lower-risk, treatment-naïve, or cytokine-refractory patient in whom sunitinib had been the de facto agent of choice, what now is the proper agent to use in this context? Should it be sunitinib or pazopanib? The efficacy data for these two agents in the largest Phase III trials to date are remarkably similar (see Table 1 for comparison of efficacy data). Both drugs were associated with a 30% objective overall response rate. The vast majority of these responses for both drugs were partial, with complete responses being relatively rare. Both agents appear to be associated with a median progression-free survival of 11 months in the treatment-naïve population.

So how are we to decide? The key may be in the differing toxicity profiles of the two agents (see Table 2). In particular, the rash and hand–foot syndrome that is often seen with sunitinib is quite rare with pazopanib. Pazopanib also appears to induce less neutropenia and lymphocytopenia than sunitinib, although this may be offset by a higher incidence of hypertension and abnormalities of aspartate transaminase and/or alanine transaminase (see Table 2). Interestingly, some work has suggested that the reduced myelosuppression with pazopanib may be due to differences in the kinase selectivity of this agent versus other TKIs, in particular less activity against Flt-3.63 Therefore, it may be that the choice of agents is determined to some degree by a patient’s comorbidities or tolerance of one agent over the other. Clearly, choosing the best therapy would be best tested in the context of a randomized trial. Fortunately, in the case of comparing sunitinib with pazopanib in the front-line setting, just such a trial is planned and ongoing (NCT00720941 at clinicaltrials.gov).39,69 The results of this trial are eagerly anticipated and should shed some light on the relative benefits and risks of these agents.

**Table 1** Comparison of efficacy data across targeted agents in phase III randomized trials

| Agent                  | Setting            | Pts (n) | OR % | PR % | CR % | PFS (mo) | OS (mo) |
|------------------------|--------------------|---------|------|------|------|----------|---------|
| Pazopanib              | Front-line (54%)   | 290     | 30   | 30   | <1   | 9.2      | –       |
|                        | Cytokine failure (46%) | 145   | 3    | 3    | 0    | 4.2      | –       |
| Placebo                |                    | 31      | 6    | 6    | 0    | 0        | 11      |
| Sunitinib              | Front-line         | 375     | 31   | 31   | 0    | 11       | 25.4    |
| IFNα                   |                    | 375     | 3     | 3    | 0    | 5        | 21.8    |
| Sunitinib              | Cytokine failure   | 451     | 10   | 10   | <1   | 5.5      | 15.7    |
| Placebo                |                    | 452     | 10    | 10   | 0    | 5.5      | 21.8    |
| Bevacizumab and IFNα   | Front-line         | 327     | 15   | 15   | 2    | 10.2     | –       |
| IFNα                   |                    | 322     | 13    | 13   | 1    | 10.2     | –       |
| Temsirolimus            | Front-line         | 209     | 8.1  | 8.1  | 0    | 3.8      | 10.9    |
| Temsirolimus and IFNα  | Poor prognosis     | 210     | 8.6  | 8.6  | 0    | 3.7      | 8.4     |
| IFNα                   |                    | 207     | 4.8  | 4.8  | 0    | 1.9      | 7.3     |
| Everolimus             | TKI failure        | 272     | 1     | 1    | 0    | 4.0      | –       |
| Placebo                |                    | 138     | 0     | 0    | 0    | 1.9      | –       |

*Note that none of these trials compared these targeted agents directly against one another in a head to head fashion; if only the comparator arm was reported and not the intervention arm, neither is included. Note also that for sunitinib and sorafenib, follow-up studies were used instead of the original Phase III trial report.

**Abbreviations:** OR, objective response rate (partial response plus complete response where both investigator and independent review results were reported, the independent review is presented); PR, objective partial response rate; CR, objective complete response rate; PFS, median progression-free survival; OS, median overall survival; TKI, tyrosine kinase inhibitor; IFNα, interferon-alpha; pts, patients, n, number; mo, months.
As more targeted therapeutics come online, the challenge will be to do the trials to place each of these in their proper place within the armamentarium for advanced RCC. Another TKI, axitinib (AG013736, Pfizer), is also undergoing active testing in Phase III trials in RCC (NCT00678392 and NCT00920816 at clinicaltrials.gov) although as of the time of writing these trials are both still accruing patients.

Another question that remains unanswered at this point concerns combination therapy. To this point, the targeted therapies have completed testing in combination only with IFNα. For example, bevacizumab was tested in combination with IFNα versus IFNα alone, with the combination shown to be superior. On the other hand, in the case of temsirolimus, the combination with IFNα was in fact inferior to monotherapy. To date, whether disparate targeted agents can be used reliably in combination regimens remains unclear and should only be undertaken in the context of a clinical trial. However, there are some intriguing data suggesting that pazopanib may have synergistic activity when combined with agents targeted to other kinases, such as HER1 and HER2. In an in vitro study

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**Table 2** Comparison of toxicity in phase III studies of sunitinib and pazopanib

| Parameter            | Pazopanib (n = 290) | Sunitinib (n = 375) |
|----------------------|---------------------|---------------------|
|                      | Any (%) | Grade 3 (%) | Grade 4 (%) | Any (%) | Grade 3 (%) | Grade 4 (%) |
| Diarrhea             | 52      | 3          | <1         | 53      | 5          | 0          |
| Hypertension         | 40      | 4          | 0          | 24      | 8          | 0          |
| Hair color changes   | 38      | <1         | 0          | 14      | 0          | 0          |
| Nausea               | 26      | <1         | 0          | 44      | 3          | 0          |
| Anorexia             | 22      | 2          | 0          | <10     | 0          | 0          |
| Vomiting             | 21      | 2          | 1          | 24      | 4          | 0          |
| Fatigue              | 19      | 2          | 0          | 51      | 7          | 0          |
| Asthenia             | 14      | 3          | 0          | 17      | 4          | 0          |
| Abdominal pain       | 11      | 2          | 0          | <10     | 0          | 0          |
| Headache             | 10      | 0          | 0          | 11      | 1          | 0          |
| Stomatitis           | <10     | 0          | 0          | 25      | 1          | 0          |
| Hand-foot syndrome   | <10     | 0          | 0          | 20      | 5          | 0          |
| Mucosal inflammation | <10     | 0          | 0          | 20      | 2          | 0          |
| Rash                 | <10     | 0          | 0          | 19      | 1          | 1          |
| Dry skin             | <10     | 0          | 0          | 16      | 1          | 0          |
| Skin discoloration   | <10     | 0          | 0          | 16      | 1          | 0          |
| Epistaxis            | <10     | 0          | 0          | 12      | 1          | 0          |
| Pain in limb         | <10     | 0          | 0          | 11      | 1          | 0          |
| Dry mouth            | <10     | 0          | 0          | 11      | 0          | 0          |
| Decline in EF        | <10     | 0          | 0          | 10      | 2          | 0          |
| ALT Increase         | 53      | 10         | 2          | 46      | 2          | 1          |
| AST Increase         | 53      | 7          | <1         | 52      | 2          | 0          |
| Hyperglycemia        | 41      | <1         | 0          | <10     | 0          | 0          |
| Total bilirubin increase | 36  | 3          | <1         | 19      | 1          | 0          |
| Hypophosphatemia     | 34      | 4          | 0          | 36      | 4          | 1          |
| Hypocalcemia         | 33      | 1          | 1          | <10     | 0          | 0          |
| Hyponatremia         | 31      | 4          | 1          | <10     | 0          | 0          |
| Hyponormogateminemia | 11      | 3          | 0          | <10     | 0          | 0          |
| Hypoglycemia         | 17      | 0          | <1         | <10     | 0          | 0          |
| Leukopenia           | 37      | 0          | 0          | 78      | 5          | 0          |
| Neutropenia          | 34      | 1          | <1         | 72      | 11         | 1          |
| Thrombocytopenia     | 32      | <1         | <1         | 65      | 8          | 0          |
| Lymphocytopenia      | 31      | 4          | <1         | 60      | 12         | 0          |
| Anemia               | <10     | 0          | 0          | 71      | 3          | 1          |
| Increased creatinine | <10     | 0          | 0          | 66      | 1          | 0          |
| Increased lipase     | <10     | 0          | 0          | 52      | 13         | 3          |
| Increased ALP        | <10     | 0          | 0          | 42      | 2          | 0          |
| Increased uric acid  | <10     | 0          | 0          | 41      | 0          | 12         |
| Increased amylase    | <10     | 0          | 0          | 32      | 4          | 1          |

*Note these were not compared head-to-head in these trials, therefore no P value given.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; EF, ejection fraction.
predominantly in non-small-cell lung cancer, the combination of pazopanib and lapatinib synergistically inhibited the growth of cancer cells and had activity against other kinases (such as c-Met) that ordinarily are only weak targets of these agents when used alone.70 Based on such preclinical studies, a Phase II study of this combination has been completed for advanced/metastatic breast cancer with promising results and another is underway for metastatic cervical cancer.59

Another open question in the management of metastatic RCC concerns the most appropriate therapy for patients with non-clear cell histology. The default strategy at present is to treat these patients with temsirolimus, based on its activity in the previously discussed Phase III trial.44 However, true progress in managing patients with non-ccRCC will likely depend on a better understanding of the biology of this distinct disease entity, and developing agents that are targeted to its pathobiology. Pertinent to pazopanib is again research demonstrating its activity against c-Met when combined with lapatinib, a HER1/HER2 kinase inhibitor.70 Since a subtype of papillary RCC (Type 1) is thought to be predominantly associated with aberrations in c-Met, this raises the intriguing possibility that the combination regimen of pazopanib-lapatinib may be useful for this disease. Clearly such a hypothesis must be tested in a properly executed clinical trial, but this highlights the potential of combination therapy that is rationally designed and implemented. It also points to the critical role that preclinical studies will play in prioritizing which agents to combine and the diseases in which to test these combinations.

Conclusion
ccRCC has a distinct tumor biology which hinges on aberrations of the VHL protein and the accumulation of HIFs in the tumor cell. Therapies targeted to this biology, including the TKIs, have dramatically improved the management of advanced and metastatic ccRCC. Among these, pazopanib is the latest oral, multikinase TKI to be approved for use in advanced RCC. The precise role for pazopanib relative to the other targeted agents remains to be fully elucidated, but it is likely to compete directly with sunitinib in the front-line setting for lower-risk metastatic disease. A head-to-head trial should shed further light on this important issue. Future trials will also need to address the potential utility of combination therapy and explore ways of treating non-ccRCC more effectively.

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The author reports no conflict of interest in this work.

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