Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Combination therapy for renal cell carcinoma: review of the clinical evidence

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The treatment of metastatic renal cell carcinoma has been revolutionized in recent years with the development of VEGF and mTOR targeted therapies. Individually, these agents have shown the ability to alter the natural history of this disease. While sequential single agent therapy appears to significantly prolong survival, patients still succumb to their disease eventually and further therapeutic advances are clearly needed. A detailed molecular understanding of the limits of the available therapies and the drivers of resistance to each is currently lacking. While those clinical investigations are undertaken, the field has turned its attention to the clinical evaluation of combination regimens containing individual drugs that have demonstrated efficacy in this disease. The largest number of such investigations has combined agents within the VEGF targeted class with mTOR inhibitors. However, there are reasons to believe that immunotherapy and chemotherapy combinations may also be relevant with this class of molecularly targeted agents. Although a number of recently completed clinical trials have provided insight into the limits of combination regimens built around VEGF targeted drugs, the results of several pending investigations will likely clarify the value of this approach.

Keywords: angiogenesis • combination • mTOR • renal cell carcinoma • VEGF

In 2009, renal cell carcinoma (RCC) was predicted to account for 58,000 new cases and nearly 13,000 deaths [1]. For patients who present with locally advanced disease the 5-year survival is estimated at 66% [1]. However, up to 40% of those who present with localized disease will develop metastases [2,3], and the 5-year survival in metastatic disease is still less than 20% [4,5].

In recent years an improved understanding of RCC tumor biology has translated into major advancements in the treatment of patients with metastatic RCC. Several new molecularly targeted agents have been identified that have led to significant improvements in progression-free survival and a general increase in overall survival, though not clearly reflected within the context of any one clinical trial. These novel therapies include inhibitors of the VEGF pathway (e.g., sunitinib, sorafenib, bevacizumab and pazopanib) and inhibitors of the mTOR pathway (e.g., temsirolimus and everolimus).

The hypervascularity observed in RCC tumors, which is driven by the inactivation of the *VHL* gene, provided a rationale for targeting angiogenesis, in particular VEGF in this disease. Biallelic inactivation of the *VHL* gene is observed in the majority of sporadic clear cell RCC tumors as a result of either mutation or promoter hypermethylation [Kim, 2004]. The product of this gene (pVHL) functions as a tumor suppressor protein by binding to the hydroxylated form of 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

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proteins such as VEGF, PDGF-β and TGF-α [George, 2003]. VEGF, an important proangiogenic factor, is overexpressed in the vast majority of RCC tumors, [Takahashi, 1994; Paradis, 2000] and its expression levels correlate with tumor stage as well as prognosis [Jacobsen, 2004]. Therefore, both its natural history and apparent genetic/physiologic dependency on VEGF-driven tumor vascularization, point to VEGF as a rational target in RCC.

The PI3 kinase pathway has been linked to the pathophysiology of RCC at the genetic and signal transduction level. Tuberous sclerosis complex (TSC)-1 and -2, one of the downstream effecters of activated PI3 kinase, is inactivated, and therefore is implicated as a tumor suppressor gene, in familial clear cell RCCs [6]. TSC2 has been linked to HIF-α expression and VEGF production, and a substantial element of the effect is mediated by mTOR [7,8]. Since restoration of a tumor suppressor gene function is not currently possible with pharmacologic approaches, interventions targeting this axis focus on signaling molecules, which are activated as a consequence of TSC loss, such as mTOR. In numerous cancer models, it has been demonstrated that mTOR inhibitors decrease HIF-α levels [9,10]. The elucidation of these key tumor and stromal cell signaling events has provided a rational basis for drug development strategies in RCC (Figure 1).

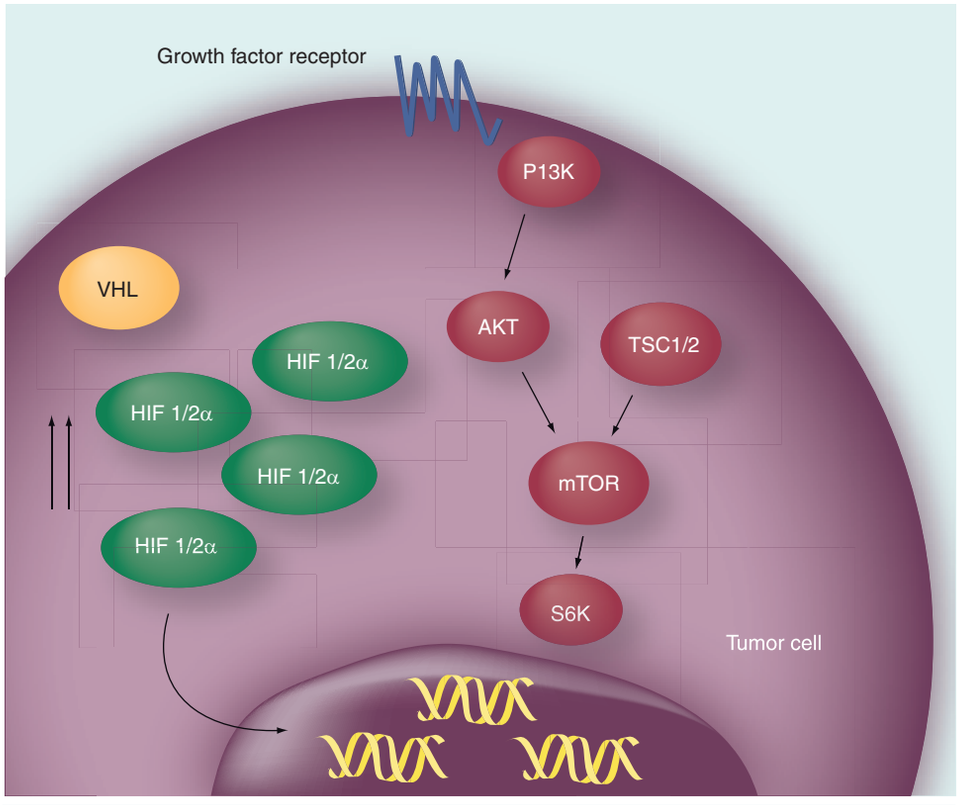

Figure 1. Title. A renal cell carcinoma cell with the PI3 kinase pathway, of which mTOR is a constituent, and the relationship of VHL loss to increased HIF1a and HIF2a. Temsirolimus and everolimus inhibit mTOR signaling and decrease HIF expression as one apparent element of their mechanism of action.

Treatment of mRCC with single agents

■ VEGF targeted therapies

This group of agents fall into three categories: agents that bind and deplete VEGF, antibodies that bind the extracellular domain of VEGF receptor and ATP-competitive small molecule inhibitor of the intracellular kinase domain of VEGF receptors. US FDA approvals have only been achieved by one agent in the VEGF ligand binding class and three drugs in the VEGF receptor tyrosine kinase class.

Sunitinib was compared with interferon (IFN) in the first line setting, exclusively for patients with clear cell RCC, in a randomized Phase III trial in which the overall response rate was 31% and median progression-free survival 11 months for sunitinib compared with response rate 6% and median progression-free survival 5 months with IFN, $p < 0.001$ [11]. Overall survival assessed in a follow-up of this study similarly showed significant benefit from sunitinib treatment among patients with high-risk features[12].

More recently, combination therapy with bevacizumab and IFN has been evaluated in two randomized Phase III trials in advanced clear cell RCC [13,14]. In the first, 649 previously untreated patients were randomized to receive either IFN-α2a in combination with bevacizumab or placebo, and in the second 732 previously untreated patients were randomized to receive bevacizumab plus IFN or IFN alone. Overall survival was the primary end point in the first trial, and was a secondary end point in the second trial, but was not significantly improved in either. However, both studies reported significant improvement in progression-free survival (the primary end point of the first trial), from 5.2 to 8.5 months ($p < 0.0001$) [13], and from 5.2 to 10.2 months ($p = 0.0001$)[14].

Pazopanib, an oral multikinase angiogenesis inhibitor, has shown efficacy in a placebo-controlled Phase III trial in treatment-naive and cytokine-pretreated patients

with metastatic clear cell RCC [15]. Compared to those treated with placebo, progression-free survival increased 4.2 to 9.2 months in those with pazopanib (HR 0.46, 95% CI: 0.34–30.62; p < 0.0000001). This benefit was seen among both the treatment-naive and cytokine-pretreated populations, although more pronounced in the treatment naive population.

Sorafenib, another orally available broad-spectrum VEGF receptor inhibitor and PDGF receptor inhibitor, was compared with placebo in a cytokine refractory population of 900 metastatic clear-cell RCC patients [16]. A nearly twofold increase in median progression-free survival was observed (5.5 vs 2.8 months, with a corresponding hazard ratio of 0.44; p < 0.001 for both comparisons). At the time of the first interim analysis, risk of death from RCC was significantly reduced by 28% (p = 0.02). A total of 10% of the sorafenib treated patients achieved a partial response.

■ mTOR inhibitors in the treatment of mRCC

Temsirolimus, a mTOR kinase inhibitor, was evaluated in a Phase III trial that randomized patients with poor prognostic features to temsirolimus alone or combination temsirolimus plus IFN compared with standard IFN [17]. Patients were permitted to have any RCC histology. Inclusion criteria consisted of at least three of six predictors of short survival as defined by the Cleveland Clinic [18]. A total of 74% of patients were classified as poor risk by the more restrictive MSKCC model with the remainder being considered of intermediate risk. Results demonstrated improved overall survival and progression-free survival in participants who received temsirolimus alone, median overall survival 10.9 versus 7.3 months with IFN alone (p < 0.0001). Median progression-free survival was 3.1 months IFN, 5.5 months temsirolimus and 4.7 months combination. There were no significant differences in objective response rates, 4.8% IFN, 8.6% temsirolimus, versus 8.1% combination. However, disease control rate including stable disease, was significantly higher in the temsirolimus arm (32.1%) compared with the IFN arm (15.5%; p < 0.001 for the comparison). There were also fewer patients with grade 3 and 4 toxicities in the temsirolimus arm (p = 0.02) [17]. Based on these results, temsirolimus was granted FDA approval for treatment of advanced RCC in 2007.

Everolimus was approved for treatment of metastatic clear cell RCC in the second line setting based on results of a Phase III placebo-controlled trial published in 2008. All participants in this study had disease that progressed following sorafenib and/or sunitinib therapy [19]. This study was stopped early after results of the second interim analysis showed a significant delay in progression-free survival from 1.9 months in the placebo arm to 3.9 months in the everolimus arm. A significantly prolonged progression-free survival was observed even amongst patient who had failed both sorafenib and sunitinib.

Considerations for combination of individually effective treatments for metastatic RCC

Although the VEGF and mTOR targeted agents are categorized separately based on their primary molecular targets, it remains unclear to what degree their ultimate mechanism of action differs. Bevacizumab, sorafenib, sunitinib and pazopanib have all been associated with decreased tumor vascularity, with a particularly significant reduction in the number of small caliber, immature tumor blood vessels in animal models of cancer [20–23]. However, similar evidence has been generated for the mTOR inhibitors as well [10]. Such an effect appears to be the result of the regulation of HIF expression by mTOR. Through this mechanism, mTOR inhibitors cause decreased expression of proangiogenic cytokines, including VEGF. At the same time, there is evidence that the antiangiogenic effects of each class of therapy are distinct when examined in preclinical models [24]. When considering the actual molecular targets of VEGF and mTOR inhibitors, combination regimens containing a drug from each class are referred to as horizontal combinations, whereas combinations of VEGF ligand- and receptor-targeted drugs are termed vertical blockade. Similarly, combinations of agents targeting other unique signal transduction pathways are classified as horizontal.

■ Combination therapy: horizontal blockade

Knowing that tumor angiogenesis is driven by numerous proangiogenic cytokines produced by the tumor, simulation of several cell types within the tumor stroma and numerous signal transduction pathways within those cells, it is hypothesized that simultaneous targeting of more than one element of the angiogenic signaling would improve upon the effects of single agent therapies (Figure 2). However, it has become increasingly clear that the same pathways are important to normal tissue homeostasis even in fully mature adults. Thus, increased toxicity can be expected for any targeted therapy combination in which the agents are administered at their individual maximum tolerated doses. Nonetheless, acceptable toxicity and promising clinical activity have been reported for some horizontal blockade strategies.

Preclinical data suggested that EGF receptor signaling contributed to tumor angiogenesis, beyond the well described effects on tumor cell proliferation [25]. As EGF receptor inhibitors became available for clinical evaluation, investigations were undertaken combining EGF receptor inhibitors with VEGF targeted therapy. An initial, single arm Phase II trial combining bevacizumab

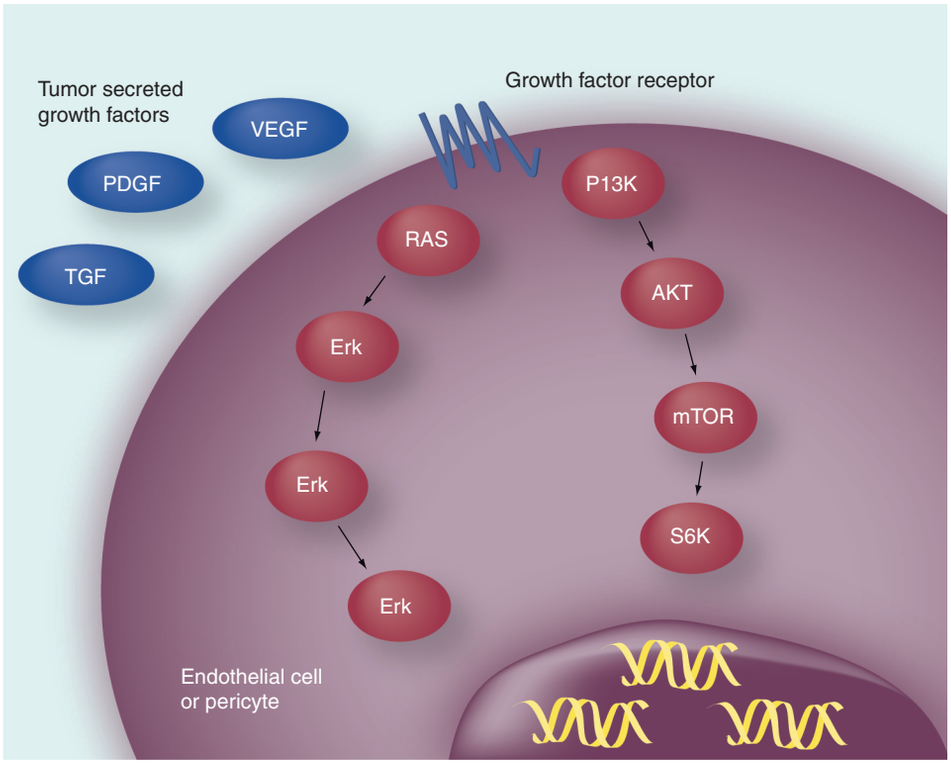

Figure 2. A vascular endothelial cell with the MAP kinase and PI3 kinase pathways lying downstream of growth factors receptors stimulated by proangiogenic factors such as VEGF, PDGF and TGF. Targeting the ligands directly or the growth factor receptors is the mechanism by which bevacizumab (direct ligand targeting) and sunitinib, pazopanib, and sorafenib (VEGF receptor tyrosine kinase inhibitors) act.

with the kinase inhibitor erlotinib appeared promising in patients with mRCC [26], a subsequent randomized Phase II trial found no significant advantage for the same combination over single-agent bevacizumab [27].

Combining bevacizumab with mTOR inhibition is also of interest and appears promising. Small, pilot Phase I/II trials demonstrated that standard doses of bevacizumab and temsirolimus could be safely combined, and reduced promising response rate to securely and treatment-naive mRCC patients [28,29]. In a randomized Phase II trial (TORAVA) in patients with treatment-naive metastatic clear-cell RCC, 88 patients received a combination of bevacizumab (10 mg/kg intravenously [iv.] every 2 weeks) and temsirolimus (25 mg iv. weekly), while 42 patients received single agent sunitinib (50 mg daily for 4 out of 6 weeks), and 41 patients bevacizumab (10 mg/kg iv. every 2 weeks) combined with three-times weekly subcutaneous IFN [30]. The percentage of patients who were progression-free at week 48 was the primary point. Progression-free rate was 43% for the bevacizumab–temsirolimus arm, 48% for single agent sunitinib and 66% for bevacizumab–IFN. Response rates were similar across the groups. The rate of severe toxicity was highest for the bevacizumab–temsirolimus arm. While this study was too small to definitively rule out a benefit associated with the novel bevacizumab–temsirolimus combination, these results seem to question the value of pursuing this combination in Phase III trials. Additional studies of first-line (NCT00631371), (NCT00719264) and salvage (NCT00651482) treatment of patients with mRCC with the combination of bevacizumab and mTOR inhibitors are ongoing.

Table 1. Phase III trials of targeted therapy in advanced renal cell carcinoma.

Agent	Trial (year)	Size (n)	% poor risk	Overall PFS (months) (95% CI)	Overall response rate (%) (95% CI)	Overall disease control rate (%)	Ref.
Sunitinib	Motzer (2007)	750	6.4	11 (10–12)	31 (26–36)	79	[xx]
Sorafenib	Escudier (2007)	903	0	5.5	1	62 (57–66)	[xx]
Temsirolimus	Hudes (2007)	626	74	5.5 (3.9–7.0)	8.6 (4.8–12.4)	32.1 (25.7–38.4)	[xx]
Everolimus	Motzer (2008)	410	15	4.0 (3.7–5.5)	1	64	[xx]
Bevacizumab/IFN	Escudier (2008)	649	9	10.2	31	77	[xx]
Bevacizumab/IFN	Rini (2008)	732	10	8.5 (7.5–9.7)	25.5 (20.9–30.6)		[xx]

IFN: Interferon; PFS: Progression-free survival.

Combination of sunitinib and temsirolimus was attempted in a Phase I trial, but was terminated after combined doses of temsirolimus 15 mg iv. weekly and sunitinib 25 mg/day could not be safely administered [31]. The combination of sorafenib and temsirolimus was studied in a Phase I trial amongst patients with advanced cancer [32]. Tolerable combination doses were, ultimately, determined to be sorafenib 200 mg twice-daily and temsirolimus 25 mg iv. weekly, again limited by the occurrence of toxicities associated with either agent alone, but more severe. With the mix of patients included in this Phase I trial, it was not possible to discern any augmentation in clinical activity beyond what one would expect to see with single-agent therapy with either drug.

■ Combination therapy: vertical blockade

Combinations of bevacizumab with other VEGF signaling inhibitors might be expected to display improved efficacy through blockade of the angiogenic pathways at multiple points (Figure 2). There is clinical evidence from Phase II trials that some of the VEGF targeted therapies maintain efficacy even in patients who have previously progress on a different VEGF targeted agent [33,34]. This suggests that cross-resistance may minimal and it is clear that the toxicity profiles of bevacizumab and TKIs are largely nonoverlapping. In addition, it has been noted that serum VEGF levels rise significantly with the initiation of VEGF receptor inhibitors such as sorafenib and sunitinib [35,36]. This could plausibly drive signaling through receptors that can be activated by VEGF, other than VEGFR2, of which VEGFR1 is an example. These observations supported the conduct of Phase I trials with bevacizumab combined with either sunitinib or sorafenib. A Phase I trial of bevacizumab (10 mg/kg iv. every 2 weeks) combined with sunitinib (escalating doses from 25 to 50 mg/day for 4 out of 6 weeks) for patients with mRCC found that although efficacy was noted (overall response rate of 52%), the regimen was poorly tolerated, with a high proportion of patients experiencing grade 3–4 toxicities requiring dose reductions or study discontinuation [37]. A subset of patients were treated for several months duration developed laboratory evidence of microangiopathic hemolytic anemia, which is consistent with endothelial cell injury in normal tissue and has been rarely observed with any single-agent antiangiogenic therapy. The sunitinib 50 mg/bevacizumab 10 mg/kg dose combination was not recommended for further study. A separate Phase I trial of this combination was conducted in patients with advanced solid tumors, only a subset of whom had RCC. This trial found that sunitinib 50 mg and bevacizumab 10 mg/kg could be combined more safely and was defined as the maximum tolerated dose, but was still associated with a significant rate of severe toxicity [38]. A total of 87% percent of patients experienced severe toxicity across the range of doses levels evaluated (hypertension [47%], fatigue [24%], thrombocytopenia [18%], proteinuria [13%] and hand–foot syndrome [13%]). In addition, patients who received higher doses of both agents required dose reductions to be able to continue on therapy beyond the first cycle. There were no observed cases of microangiopathic hemolytic anemia, however, this trial was distinguished from the previous studies in that it was not conducted in patients with renal dysfunction that is typically characteristic of patients who have undergone nephrectomy and the average duration of treatment was significantly shorter because the combination produced limited efficacy in this mixed patient population.

Similarly, tolerability problems have been noted for the combination of bevacizumab with sorafenib in treating patients with solid tumors [39]. Sorafenib 200 mg orally twice-daily and bevacizumab intravenously at 5 mg/kg every 2 weeks were the maximum tolerated doses, and ultimately the investigators determined that a 2-day interruption in sorafenib dosing out of every seven was needed to be able to administer this combination. Nearly three quarters of the patients required a dose reduction to 200 mg/day of sorafenib in order to continue on therapy beyond four cycles. Grade 3 proteinuria and thrombocytopenia were the dose limiting toxicities. A total of 13 patients with advanced ovarian cancer who had failed multiple prior therapies were treated and six of them (43%) achieved a partial response. Despite significant limitations in the dose and dose intensity of the combined regimen, significant

Table 2. Ongoing combination therapy trials in renal cell carcinoma.

Trial name	Sponsor	Accural goal	Arms	Phase	Primary end point	NCI number	Ref.
BeST (E2804)	ECOG	360	Bev Bev + Tem Bev + Sor Sor + Tem	II	PFS	NCT00378703	[xx]
INTORACT	Pfizer	800	Bev + Tem Bev + IFN	III	ORR and OS	NCT00631371	[xx]
Record-2	Novartis	360	Bev + Ev Bev + IFN	II	PFS	NCT00719264	[xx]

Bev: Bevacizumab; Ev: Everolimus; IFN: Interferon; OS: Overall survival; PFS: Progression-free survival; Sor: Sorafenib; Tem: Temsirolimus.

clinical activity was observed treated given that single agent bevacizumab as previously been associated with significant activity as well, the contribution of sorafenib to it would require further study in this context.

A separate Phase I trial combining sorafenib and bevacizumab has been conducted exclusively in patients with metastatic RCC and preliminary results reported [40]. 48 patients were accrued to the range of doses, with the maximum tolerated dose being determined at 200 mg daily of sorafenib combined with bevacizumab 5 mg/kg intravenously every 2 weeks. With higher doses of either agent, an increased incidence of the toxicities typically observed with either agent alone was noted, including hypertension, rash, proteinuria and hand–foot syndrome. Nonetheless, only four patients failed to demonstrate evidence of tumor regression early in the course of therapy. The objective response rate was 52% and median progression-free survival was 14 months. Again, despite having to compromise the doses of either agent in the combination, antitumor activity and disease control were observed that were both outside the bounds of what has previously been seen in numerous single agent sorafenib or bevacizumab Phase II and III trials.

The available evidence from bevacizumab/sunitinib and bevacizumab/sorafenib combinations suggest that blockade of two points of VEGF signaling amplifies toxicities thought to be mediated by inhibition of these targets in normal tissue. It would appear that these combination regimens are pushing the envelope of therapeutic index that can be achieved with such a high degree of pathway inhibition. Notably, both sorafenib and sunitinib have a broad spectrum of targets beyond VEGF receptors. These include PDGF receptor amongst others. It is possible that more selective VEGF receptor inhibitors could be safely and effectively combined with a very selective VEGF ligand targeted agent such as bevacizumab. However, such investigations have not yet been initiated.

Both vertical & horitzontal blockade: BeST trial

In the Eastern Cooperative Oncology Group (ECOG) a randomized Phase II trial has completed accrual which simultaneously evaluates three of the regimens discussed above among patients with metastatic clear-cell RCC: bevacizumab/temsirolimus, bevacizumab/sorafenib, sorafenib/temsirolimus (NCT00378703). A single agent bevacizumab arm was included as a simultaneous benchmark cohort with single agent therapy. Bevacizumab was chosen partly because its single agent activity is a first-line therapy for metastatic RCC has not been fully characterized, as well as the fact that it is a component of two of the combination regimens. 90 patients are to be accrued each on, and the goal of the trial is to identify the combination regimen that is associated with a median progression-free survival of 14 months or more, which would be taken as sufficient evidence to support a subsequent randomized trial compared with standard of care. With accrual completed, the outcome data should be mature by late 2012.

Combination therapy: immunotherapy

Several clinical trials have investigated the potential positive interaction between IFN with VEGF targeted therapy. As noted above, the Phase III trial that established the benefit of bevacizumab in metastatic RCC combined bevacizumab with interferon [14]. As there was no single-agent bevacizumab arm in that trial, it remains uncertain what stand-alone contribution bevacizumab made to improved progression-free survival as opposed to a mechanistic interaction with interferon. Notably, the temsirolimus trial contained a combination temsirolimus–IFN arm which faired no better than the single-agent interferon arm with regard to overall survival or progression-free survival [17]. Sorafenib has also been investigated in combination with IFN in three Phase II trials [41–43]. In one single-arm trial the response rate and progression-free survival appeared promising in comparison to data from other sorafenib trials, but in the other two there was no discernable difference. Thus, bevacizumab is the only one for which there is definitive evidence of benefit from an IFN-containing combination, but even there it is not clear that interferon is adding significantly. There has been relatively little enthusiasm in the research community to further investigate combinations with IFN owing to its toxicities and limited single-agent activity.

Although the role of low-dose single-agent cytokines is limited in patients with mRCC, combinations of cytokines with targeted therapy may have merit. Bevacizumab and IL-2 have been combined in a CWG trial. Preliminary results suggest that these two agents can be given safely in combination and produce efficacy improvements that are additive but not synergistic [44]. As previously described, two large Phase III trials of interferon plus bevacizumab vs interferon alone have demonstrated superior efficacy with the combination regimen compared with cytokine monotherapy and suggest the potential of an additive effect [14,45]. Confirmation of the benefit of combination therapy will require a randomized trial comparing the combination to bevacizumab alone.

Chemotherapy-based - combination therapy

While RCC is considered highly resistant to chemotherapy, gemcitabine-containing regimens have shown some efficacy in patients with tumors containing sarcomatoid features with response rates of 5–17% [46]. Nanus and colleagues reported on 18 patients, 56%

with sarcomatoid advanced RCC, treated with combination doxorubicin 50 mg/m^2 and gemcitabine 1500 or 2000 mg/m^2 every 2 to 3 weeks with granulocyte-stimulating factor support[47]. Four of the 11 patients with sarcomatoid disease experienced a tumor response, and two additional patients experienced disease stability. The two patients in this study who experienced a complete remission both had sarcomatoid histology. This combination was further studied in ECOG 8802, a Phase II trial involving patients with tumors containing greater than 25% sarcomatoid features[48]. Of 38 patients treated, there were seven documented responses, one undocumented, and nine patients with stable disease. Median overall survival was 8.8 months. Taken together, these studies suggest that gemcitabine-containing regimens may offer some benefit in treating patients with sarcomatoid variant RCC.

VEGF pathway inhibitors have been tested in combination with chemotherapy agents in other solid tumors with regimens containing bevacizumab showing efficacy in patients with breast, colon, lung and brain cancers [49–54]. Michaelson *et al.* studied the combination of sunitinib plus gemcitabine in 34 patients with advanced RCC and noted antitumor activity in 19 [55]. Of the nine patients with poor risk or high-grade RCC, five experienced a partial response. Grade four adverse events, including one myocardial infarction, one pulmonary embolism and two patients with severe neutropenia, were observed in four patients. Results of this Phase I study suggest that sunitinib in combination with gemcitabine may be active in patients with poor risk profiles and/or sarcomatoid histology, and a Phase II study is underway to more clearly assess the efficacy of this combination (NCT00556049). Bevacizumab in combination with gemcitabine and capecitabine is also currently being evaluated in metastatic RCC (mRCC; NCT00496587).

Future perspective

In some respects, progress towards identifying the most rational combination regimens in RCC has been limited by the difficulty in obtaining tumor biopsies to inform molecular mechanisms of resistance. This is not a problem unique to RCC, but with many other metastatic solid tumors in which sites of metastatic disease are typically deep in visceral organs and not readily accessible for minimally invasive biopsies. Furthermore, the complexity of measuring angiogenesis in a quantitative way has not been resolved, even in experimental systems. It is known that heterogeneity within any given primary or metastatic tumor will produce variable results depending on which portion of the tumor is biopsied. For these reasons, it is hoped that blood-based assays will give insight into adaptations in angiogenic signaling in the midst of treatment with the available therapies. Such methods could be used to nominate rational combination strategies for the next generation of clinical trials. In the meantime, the principle of establishing a single agent activity prior to initiating combination regimens dictates, which drugs have been investigated in this way.

It should be recognized that the current default in clinical management is to patients with single-agent VEGF- or mTOR-targeted therapy, with the exception of the bevacizumab/interferon combination. Given that early clinical results indicate increased toxicity even with reduced doses of individual agents used in combination, a significant enhancement in clinical activity will be needed to justify the routine clinical use of combinations over sequential single agent therapy. Nonetheless, current investigations in this area will hopefully provide further insight into the mechanisms underlying angiogenesis in RCC, a tumor which seems uniquely driven by this biology.

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Executive summary

- A deep understanding of the molecular pathophysiology of renal cell carcinoma (RCC) has emerged within the past decade, demonstrating its unique dependency on aberrant VHL/HIF regulation of angiogenesis.
- Individual VEGF and mTOR targeted therapies clearly delay disease progression in metastatic RCC compared with no therapy or the historical treatment standard, interferon.
- Preclinical and clinical evidence of early support an antiangiogenic mechanism for each of the effective therapies developed in the past several years.
- The precise molecular mechanisms that mediate resistance to VEGF- and mTOR-targeted therapies in RCC have not yet been elucidated.
- Combination regimens built around VEGF targeted therapies are being developed with the hope of stemming the benefit offered by the first generation of single-agent targeted therapies.

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