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Treatment Options in Metastatic Renal Cell Carcinoma: Focus on mTOR Inhibitors

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Abstract: The agents currently approved for use in metastatic renal cell carcinoma (mRCC) can be divided broadly into two categories: (1) vascular endothelial growth factor receptor (VEGFR)-directed therapies or (2) inhibitors of the mammalian target of rapamycin (mTOR). The latter category includes everolimus and temsirolimus, both approved for distinct indications in mRCC. Everolimus gained its approval on the basis of phase III data showing a benefit in progression-free survival relative to placebo in patients previously treated with sunitinib and/or sorafenib. In contrast, temsirolimus was approved on the basis of a phase III trial in treatment-naïve patients with poor-risk mRCC, demonstrating an improvement in overall survival relative to interferon-alfa. While these pivotal trials have created unique positions for everolimus and temsirolimus in current clinical algorithms, the role of mTOR inhibitors in mRCC is being steadily revised and expanded through ongoing trials testing novel sequences and combinations. The clinical development of mTOR inhibitors is outlined herein.

Keywords: metastatic renal cell carcinoma, mRCC, mTOR inhibitors

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Introduction

The management of metastatic renal cell carcinoma (mRCC) has been revolutionized by the advent of targeted therapies. A decade ago, use of immunotherapy predominated. Agents such as interleukin-2 (IL-2) have demonstrated the potential to generate durable complete responses (CRs), albeit in a relatively small proportion of patients (<10%).¹ Another oft-used immunotherapeutic strategy, interferon- α (IFN- α), led to only modest improvements in clinical outcome when compared in randomized trials to supportive drugs such as medroxyprogesterone.² Despite these sobering results, it was recommended in 2002 that IFN- α represent the comparator arm in future studies of targeted agents.³ Since that time, the landscape of mRCC therapy has changed dramatically, with a total of six novel agents approved for this indication. Of these agents, four antagonize signalling via the vascular endothelial growth factor receptor (VEGFR), either by consumption of ligand (i.e. bevacizumab) or inhibition of the tyrosine kinase domain (i.e. sunitinib, sorafenib and pazopanib).^{4–8} In contrast to these VEGFR-directed therapies, the remaining two agents, everolimus and temsirolimus, antagonize signalling via the mammalian target of rapamycin (mTOR).^{9,10} Outside of a distinct mechanism, these agents have unique considerations with respect to both safety and efficacy. Herein, the clinical development of mTOR inhibitors and their current application in mRCC is outlined.

Mechanism of Action

mTOR is a serine/threonine kinase measuring 289 kDa, and is a member of the phosphatidylinositol-3-phosphate (PI3K) family of proteins.¹¹ These PI3K family proteins play a role in cell cycle checkpoint regulation through a variety of mechanisms.¹² Activation of Akt, as noted in Figure 1, is initially triggered first by interaction of an extracellular ligand with a transmembrane receptor tyrosine kinase.^{13,14} Autophosphorylation of the internal domain of the kinase triggers activation of PI3K, subsequently activating Akt. Activation of Akt is potentially abrogated by the tumor suppressor phosphatase and tensin homologue gene on chromosome 10 (PTEN).¹⁵ Frequently, loss of PTEN results in increased Akt-mediated signalling and enhanced cell growth and division. Downstream of Akt are the tuberous sclerosis complexes 1 and 2 (TSC1 and TSC2).^{16,17} These moieties

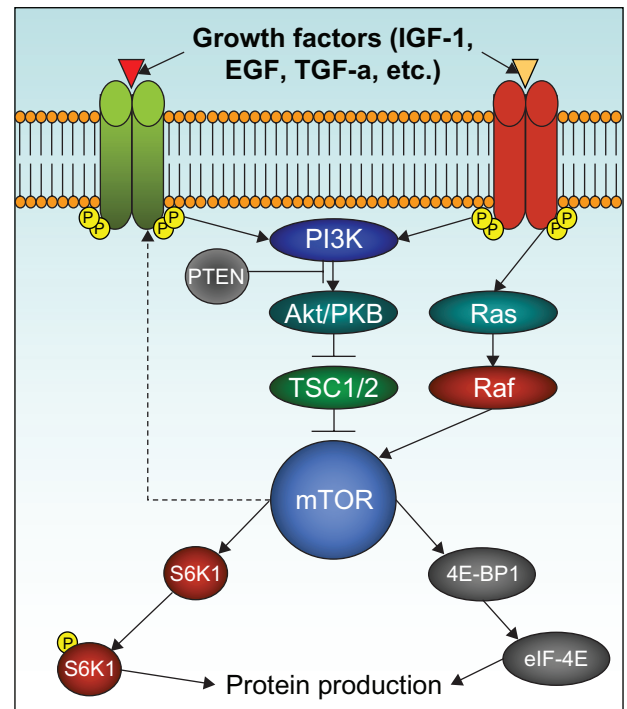


Figure 1. Signalling via mTOR relevant to renal cell carcinoma pathogenesis. (Adapted with permission from Pal SK, Figlin RA, Reckamp KL: The role of targeting mammalian target of rapamycin in lung cancer. *Clin Lung Cancer* 9:340–5, 2008.)

are inhibited by Akt, releasing inhibition on the mTOR complex downstream. Two distinct complexes of mTOR exist, mTOR_{c1} and mTOR_{c2}—only the former is susceptible to inhibition by rapamycin analogues.¹⁸ When activated, mTOR_{c1} triggers increased transcription via several mediators, including p70S6K and 4E-BP1.¹⁹ As opposed to abrogating mTOR kinase activity, the mTOR inhibitors prevent the association of mTOR and mLST8 in the mTOR_{c1} complex at pharmacologically achievable doses, thereby inhibiting downstream signalling.²⁰

Temsirolimus

Single agent temsirolimus: Phase I data

The Developmental Therapeutic Branch of the National Cancer Institute first identified the antitumor activity of temsirolimus.²¹ In preclinical models, it appeared that the agent decreased proliferation of murine xenografts bearing various solid tumors, including glioma, breast and prostate cancer.^{22–24} In a phase I trial evaluating temsirolimus in patients with advanced cancer, 24 patients were treated at doses ranging from 7.5 to 220 mg/m² intravenous weekly.²⁵ Doses limiting toxicities (DLTs) were observed at



220 mg/m², including acneiform rash, stomatitis and mucositis, all of which resolved after discontinuation of therapy. Pharmacokinetic data from the study indicated that a flat dosing schema was appropriate for the agent. In this preliminary experience, confirmed partial responses (PRs) were observed in two patients with mRCC and breast cancer, respectively. Notably, the patient with mRCC had documented progression with prior IL-2 and IFN- α therapy.

Temsirolimus in combination with other agents approved for mRCC

Relevant to the therapy of mRCC, several phase I experiences have assessed the combination of temsirolimus with other VEGFR-targeted therapies. Fischer et al reported a trial sunitinib and temsirolimus in patients with refractory mRCC.²⁶ Unfortunately, two DLTs were noted within the first cohort of three patients using a starting dose of temsirolimus of 15 mg intravenous weekly and sunitinib 25 mg oral daily (on a conventional 4 week on, 2 week off regimen). In light of the low starting dose with these compounds, the study was ultimately abandoned.

The combination of temsirolimus and bevacizumab appears to be better tolerated in the context of mRCC.^{27,28} In a phase I/II study, patients with clear cell mRCC that had progressed on up to 2 prior regimens were enrolled. In the phase I component, a best response of PR was observed in seven patients amongst a total of 12 evaluable patients.²⁷ DLTs incurred in the phase I component included hypertriglyceridemia and mucositis, and a recommended phase II dose of bevacizumab 10 mg/kg intravenously every 2 weeks with temsirolimus 25 mg intravenously every week was established. With data available for 35 of 40 patients in the phase II experience, 4 patients (16%) had PRs and 18 patients (72%) had SD.²⁸ Given the considerable clinical benefit, a phase IIIb trial has been launched to assess this regimen. In the INTORACT study, a total of 800 patients will be randomized to either bevacizumab with everolimus or bevacizumab with temsirolimus.²⁹

Although little data is available for the combination of sorafenib and temsirolimus in mRCC, a phase I/II trial in melanoma has assessed this regimen. In this trial, patients with stage IV or unresectable melanoma were treated with sorafenib twice daily with weekly intravenous temsirolimus.³⁰ In this study, a maximally tolerated dose (MTD) of sorafenib 600 mg oral daily

with temsirolimus 25 mg intravenous weekly was identified. With 21 evaluable patients, 9 patients had stable disease (SD)—no responses were recorded. DLTs observed in this study were thrombocytopenia, hand-foot syndrome (HFS), liver function test (LFT) abnormalities and hypertriglyceridemia. Notably, this combination have been incorporated in the randomized, phase II BeST study in mRCC.³¹

In a phase I/II study, temsirolimus was combined with IFN- α in 71 patients with mRCC.³² In this study, the recommended phase II dose was ultimately temsirolimus 15 mg intravenous weekly and 6 million units (MU) of IFN- α administered subcutaneously three times per week in light of stomatitis, fatigue and nausea/vomiting observed at higher doses. In 39 patients treated at this recommended dose, PRs were observed in 8% of patients and SD \geq 24 weeks was observed in 36% of patients, with a median progression-free survival (PFS) of 9.1 months. A phase III experience with temsirolimus in mRCC is described subsequently.^{10,33}

Temsirolimus with other targeted agents

A phase I/II study assessed erlotinib with temsirolimus in patients with recurrent malignant gliomas.³⁴ The phase I component of this trial enrolled 22 patients, with DLTs of rash, mucositis and LFT abnormalities occurring beyond the MTD (determined to be erlotinib 150 mg oral daily with temsirolimus 15 mg intravenous weekly). Temsirolimus with hormonal therapy (i.e. letrozole) has also been assessed in the setting of metastatic breast cancer. In a phase II study including 92 heavily pre-treated patients, the combination resulted in a clinical benefit rate (complete response, CR, plus PR plus SD) of 82%.³⁵

Phase III data for temsirolimus in mRCC

The encouraging data for temsirolimus as a single agent or with IFN- α in mRCC spurred a pivotal phase III trial. In this study, a total of 626 treatment-naive patients were identified with poor-risk features (defined in Table 1). Importantly, the study was open to all histologic subtypes, and further allowed patients who had treated brain metastases. Patients were randomized to one of three arms: (1) temsirolimus alone, (2) temsirolimus with IFN- α , or (3) IFN- α . Patients in the IFN- α group received 3 MU subcutaneously three times weekly, titrated up to a dose of 18 MU.



Table 1. Predictors of poor survival used in the pivotal, phase III study of temsirolimus to define study candidates. For enrolment, at least three of the six predictors were required.¹⁰

Poor-risk criteria

1. Serum LDH > 1.5 times the ULN
2. Hemoglobin level < LLN
3. Corrected serum calcium level > 10 mg/dL (2.5 mmol/L)
4. Time from initial diagnosis of renal-cell carcinoma to randomization < 1 year
5. Karnofsky performance score of 60 or 70
6. Metastases in multiple organs

The group receiving temsirolimus alone received the agent at a dose of 25 mg intravenous weekly. Finally, in the combination arm, patients received temsirolimus at 15 mg intravenous weekly, with a starting dose of 3 MU of IFN- α titrated up to 6 MU subcutaneously three times per week. This dose was established in an aforementioned phase I/II study.³²

The primary endpoint of this study was overall survival (OS). When compared to the IFN- α alone arm, little difference in OS was observed with combination therapy (hazard ratio, HR, 0.96, 95% CI 0.76–1.20; $P = 0.70$). In contrast, median OS improved from 7.3 to 10.9 months in the comparison of IFN- α to temsirolimus alone (HR 0.73, 95% CI 0.58–0.92; $P = 0.008$). Response rates (RRs) did not differ significantly between treatment arms, amounting to an overall RR of <10% in all groups. The reported OS data have led to a category 1 recommendation from the National Comprehensive Cancer Network (NCCN) for use of temsirolimus in poor-risk patients.³⁶ Key elements of the study are summarized in Table 2.

Everolimus

Single agent everolimus: Phase I data

Prior to the report of everolimus activity in cancer, the agent had been extensively studied in the setting of cardiac and renal transplantation.^{37,38} An initial phase I trial in advanced solid tumors explored both weekly and daily dosing of oral formulations of the drug.³⁹ In the first phase, patients were treated with weekly doses ranging from 5 to 30 mg. No DLTs were observed, and accompanying correlative studies assessing peripheral blood mononuclear cells (PBMCs) showed downregulation of relevant downstream moieties (i.e. p70S6K). In the second part of the study, patients were treated with weekly doses of everolimus above 30 mg and daily doses of 5 or 10 mg. Although the half-life of everolimus (~30 hours) was thought to facilitate weekly dosing of the drug, it was observed that daily dosing could produce more sustained target inhibition in preclinical models.⁴⁰ Ultimately, it was determined that doses of 70 mg weekly and 10 mg daily could be satisfactorily tolerated.

Everolimus in combination with other agents approved for mRCC

Like temsirolimus, everolimus has been explored in a number of combinations with other cytotoxic and targeted agents. The combination of everolimus and sorafenib has been assessed in a disease-specific phase I trial in patients with mRCC.⁴¹ Patients in this study had predominantly clear cell histology and had progressed on prior immunotherapeutic agents, VEGFR-directed therapies and/or everolimus. With 18 patients enrolled, the MTD (sorafenib at 400 mg oral twice daily with everolimus 10 mg daily) was identified

Table 2. Key features of the pivotal phase III trials evaluating everolimus and temsirolimus.^{10,55}

Characteristic	Temsirolimus	Everolimus
Study population	Treatment-naive patients with poor risk disease	Patients who had progressed on prior sunitinib and/or sorafenib
Number of patients	626	410
Randomization	Temsirolimus vs. temsirolimus/IFN- α vs. IFN- α	Everolimus/BSC vs. Placebo/BSC
Primary Endpoint	OS	PFS
Met primary endpoint?	Yes	Yes
Δ PFS (P -value)*	1.9 mos ($P = \text{NR}$)**	3.0 mos ($P < 0.001$)
Δ OS (P -value)	3.6 mos ($P = 0.008$)	0.39 mos ($P = 0.177$)

Abbreviation: *BSC, best supportive care.

* Δ PFS and Δ OS values reported for temsirolimus pertain to the comparison of temsirolimus alone to IFN- α . **To the author's knowledge, the P -value for this statistic has not been reported to date.



as the recommended phase II dose. DLTs incurred included pulmonary embolism, thrombocytopenia and pneumonitis. A similar trial in mRCC assessed the combination of sunitinib and everolimus.⁴² In this experience, both daily and weekly dosing strategies were examined with a consistent dose of sunitinib 37.5 mg oral daily in all cohorts. Ultimately, a dose of everolimus 20 mg oral weekly with sunitinib 37.5 mg oral daily was recommended for phase II study. Notably, amongst five patients with confirmed PRs on study, three had non-clear cell histology.

The combination of bevacizumab with everolimus has also been explored in mRCC. In a phase I study in advanced solid tumors, a recommended phase II dose of bevacizumab 10 mg/kg intravenously every 2 weeks and everolimus 10 mg oral daily was determined.⁴³ Notably, amongst 14 evaluable patients, seven had SD as a best response. A subsequent phase II study conducted in patients with mRCC enrolled a total of 59 patients. Amongst patients who completed eight weeks of treatment, 21% of patients had an objective response, and an additional 69% had SD. Notably, grade 3/4 proteinuria was seen in 19% of patients enrolled in this experience; most other toxicities were mild. As with temsirolimus, the combination of everolimus with bevacizumab is now being assessed in a randomized fashion. In the RECORD-2 study, 360 patients will be randomized to bevacizumab with either everolimus or IFN- α .⁴⁴ The estimated primary completion date is February 2012.

Everolimus with other targeted agents/cytotoxic therapy

A phase II trial of everolimus with imatinib was conducted in mRCC, with the rationale that added platelet-derived growth factor receptor (PDGFR) blockade from imatinib could contribute to the antitumor effect of everolimus.⁴⁵ With nine patients evaluable, seven had recorded PRs and two had PD. The regimen was noted to have moderate toxicity, with grade 3 toxicities including pneumonitis, angioedema, fatigue and thrombocytopenia. Notably, a phase I/II study of everolimus and imatinib in gastrointestinal stromal tumor (GIST), where PDGFR has a well-documented role in pathogenesis, has demonstrated moderate efficacy with the regimen.⁴⁶

A separate phase I effort assessed a combination of bevacizumab, everolimus and erlotinib.⁴⁷ In a cohort of 34 patients, an MTD and recommended phase II

dose of bevacizumab 10 mg/kg intravenously every two weeks, everolimus 10 mg daily and erlotinib 75 mg oral daily was determined. Notably, several severe toxicities were encountered with this regimen, including nephrotic syndrome, cardiac ischemia and ventricular thrombosis. Of two PRs seen with this regimen, one was documented in a patient with mRCC. In a similar effort combining VEGFR-, mTOR- and EGFR-directed therapy, a phase I trial has explored the combination of bevacizumab, everolimus and panitumumab in advanced solid tumors.⁴⁸ DLTs of rash and mucositis were identified using bevacizumab 10 mg/kg intravenously every 2 weeks, everolimus 5 mg oral every other day and panitumumab 4.8 mg/kg intravenously every 2 weeks. Amongst nine evaluable patients, SD was recorded as the best response in eight.

In breast cancer, several trials are examining the combination of everolimus with HER2-directed therapies. A phase I trial of everolimus in combination with paclitaxel and trastuzumab included 13 heavily pre-treated patients; all had clinical benefit (either PR or SD) at the time of an interim analysis.⁴⁹ Furthermore, DLTs had not been encountered with this regimen to date. In a more liberal phase Ib design, trastuzumab and everolimus is being examined in combination with any single chemotherapeutic agent specified by the clinician.⁵⁰ A phase I study of the dual EGFR and HER2 tyrosine kinase inhibitor lapatinib in combination with everolimus is ongoing.⁵¹

In estrogen receptor-positive breast cancer, the combination of letrozole and everolimus has been examined.⁵² No pharmacokinetic interactions were observed in 30 patients, and a standard dose of letrozole (2.5 mg oral daily) was deemed appropriate in combination with everolimus 10 mg oral daily. This phase I study was followed by a randomized phase II effort (comparing letrozole with or without everolimus) validating the clinical efficacy of this combination.⁵³

Phase III data for everolimus in mRCC

A phase II study of everolimus in mRCC used a dose of 10 mg oral daily.⁵⁴ Patients in this study were either treatment-naïve or had received only one prior therapy. Of 41 patients enrolled in this effort, 39 were evaluable for safety and 37 were evaluable for response. Clinical outcomes were impressive; median PFS and OS were 11.2 months and 22.1 months, respectively.



In total, approximately 70% of patients experienced PFS \geq 6 months.

On the basis of this encouraging data, everolimus was examined in a phase III trial in patients who had received prior sorafenib and/or sunitinib (RECORD-1).⁵⁵ In this international study, patients were randomized to receive either everolimus ($n = 272$) or placebo ($n = 138$) in a 2:1 fashion. Both treatments were administered in conjunction with best supportive care (BSC). The primary endpoint of the study was PFS. At the time of an initial data cut-off, median PFS was improved from 1.9 months in the placebo arm to 4.0 months in the everolimus arm (HR 0.30, 95% CI 0.22–0.40; $P < 0.0001$). At a six-month interval, the progression-free probability was 26% with everolimus as compared to 2% with placebo. No difference in OS was observed; median OS with everolimus and placebo were 14.78 and 14.39 months, respectively (HR 0.87, 95% CI 0.65–1.17; $P = 0.177$).⁵⁶

Safety Considerations with mTOR Inhibitors

Toxicity data from the phase III studies of temsirolimus and everolimus point to unique class effects.^{10,32} Both agents appear to affect the metabolic profile of the patient. Hypercholesterolemia (all grades) was observed in 24% of patients receiving temsirolimus and in 76% of patients receiving everolimus. Similarly, hyperglycemia (all grades) was seen in 26% and 50% of patients receiving these therapies, respectively. Although present in a relatively large proportion of patients, the severity of these toxicities was generally mild—few grade 3/4 toxicities were recorded. The mechanism by which this occurs appears to be complex. In rodent models, while it appears that rapamycin reduces *de novo* lipid synthesis, there was a parallel increase in oxygenation of exogenous lipids.⁵⁷ In the same models, decreased glycogen synthesis and non-insulin-dependent glucose transport was observed, potentially explaining the hyperglycemia observed with mTOR inhibitors. An intricate axis linking hyperglycemia, hyperlipidemia and mTOR-related signalling has also been posited. In preclinical experiments, it has been shown that rapamycin can block insulin-mediated phosphorylation of lipin.⁵⁸ Lipin (present in the setting of fatty liver dystrophy)

produces hyperlipidemia and defects in adipocyte differentiation in an insulin-dependent fashion.

The occurrence of non-infectious pneumonitis is increasingly recognized with mTOR inhibitors. The most recent presentation of data from the RECORD-1 trial suggested that 14% of patients treated with everolimus developed non-infectious pneumonitis; notably, these cases were reviewed by a team of pulmonary specialists.⁵⁶ Amongst ten patients who developed grade 3 non-infectious pneumonitis, eight patients had complete clinical resolution with steroid therapy. These data underscore the importance of early recognition of this potentially lethal toxicity. Use of imaging alone can be challenging—with serial review of radiographic imaging of 245 patients receiving everolimus and 132 patients receiving placebo, new findings were seen in a far higher percentage of patients receiving everolimus as compared to placebo (38.9% vs. 15.2%), even in the absence of a clinical diagnosis of pneumonitis.⁵⁹ Bronchoscopic evaluation should be pursued, and treatment with steroid therapy should be instituted if infectious causes are ruled out. This algorithm can also be used for temsirolimus therapy. A follow-up study of patients treated with temsirolimus in the original pivotal trial identified only four cases of pneumonitis.⁶⁰ However, in one of these cases, a patient progressed from grade 3 to 5 toxicity, with this death “possibly” attributed to therapy.

Other prominent side effects associated with mTOR inhibitors include stomatitis and rash. In trial experiences to date, these toxicities appear to be manageable with standard supportive measures.⁶⁰ Hematologic side effects have also been observed with these therapies. Published recommendations for temsirolimus suggest holding doses for absolute neutrophil counts (ANCs) of less than 1000/ μ L, platelet counts of less than 75,000/ μ L or any other grade 3/4 hematologic event.⁶⁰ These recommendations further suggest that re-initiation of therapy should occur only when the toxicity resolves to grade 2 or lower. Similar strategies can be employed for therapy with everolimus. The clinician should also be mindful of potential drug interactions in using everolimus and temsirolimus; strong inducers and inhibitors of CYP3A4 should be avoided.⁶¹ The patient should also be counselled against taking grapefruit juice, which can affect metabolism of these agents.



Optimal Sequence and Synergy

With a diverse array of treatment options, it is challenging to ascertain how the mTOR inhibitors are most placed in existing algorithms (Table 3). At the present time, use of everolimus and temsirolimus in clinical practice should parallel their use in the phase III studies leading to their approval. For instance, use everolimus should be confined to patients who are refractory to prior VEGF-directed therapy.⁵⁵ Furthermore, temsirolimus should be offered to those treatment-naïve patients that have poor-risk disease.¹⁰

Several studies may change these paradigms. For instance, the RECORD-3 trial utilizes a unique design, randomizing patients with treatment-naïve mRCC to receive either sunitinib or everolimus as initial therapy, followed by crossover to the opposite regimen (Fig. 2).⁶² The primary endpoint is PFS, and the study is powered to determine non-inferiority of either regimen. If positive, the results of this study could suggest interchangeable use of sunitinib and everolimus as first-line therapy. mTOR inhibitors may also become incorporated in first-line algorithms when used in combination with VEGFR-directed therapy (Fig. 3). The aforementioned INTORACT and RECORD-2 studies, evaluating bevacizumab in combination with temsirolimus and everolimus, respectively, may alter the current recommendation of using bevacizumab in combination with IFN- α .^{29,44} Notably, INTORACT is structured as a phase IIIb study and is expected to enroll a total of 800 patients. In contrast, RECORD-2 (a randomized phase II effort) will include approximately 360 patients. The primary completion date of both

studies is February 2012. Given the larger scope, INTORACT may have a more tangible impact on therapeutic decision-making. As previously noted, the BeST study will also include arms evaluating mTOR inhibitors in combination with VEGFR-directed therapy.³¹ Two of the four arms in this study include such a combination (sorafenib with temsirolimus, and bevacizumab with temsirolimus). However, in this randomized phase II effort, only 90 patients will be accrued to each arm.

Several questions also surround the optimal second-line therapy for mRCC. Available data suggests that actual practice patterns do not include substantial use of mTOR inhibitors as second-line therapy. In a retrospective analysis of 645 patients treated with sunitinib, sorafenib or bevacizumab up-front, a total of 218 patients received second-line therapy.⁶³ Of these, only 24 patients (11%) received either everolimus or temsirolimus; the majority received secondary VEGFR-directed treatments. The data to support re-challenge with VEGFR-directed therapy is derived largely from retrospective series, though phase II data and an ongoing phase III trial may support the use of axitinib in this setting.^{64,65} A lingering question remains in the face of this trial—does second-line therapy with an mTOR inhibitor or VEGFR-directed agent represent the superior approach? An ongoing randomized trial is comparing sorafenib to temsirolimus in patients who have failed prior therapy with sunitinib.⁶⁶ The study is expected to accrue a total of 480 patients by May of 2011. At this time, only retrospective data is available to document the activity of temsirolimus in patients who are refractory to VEGFR-directed therapy.⁶⁷

Table 3. A current, evidence-based algorithm for the management of mRCC. (Adapted from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Renal Cell Carcinoma, v.1.2010.)

Disease and line of therapy	Setting	Therapy	
		Phase III data	Phase II data
Clear cell RCC, first line	Good/intermediate risk	Sunitinib, Bevacizumab + IFN, Pazopanib	HD IL-2
	Poor risk	Temsirolimus*	
Clear cell RCC, second line	Prior cytokines	Sorafenib	Sunitinib, bevacizumab
	Prior VEGFR TKI	Everolimus	
	Prior bevacizumab		Sunitinib

*Note that in the pivotal trial of temsirolimus, all histologic subtypes of mRCC were included.

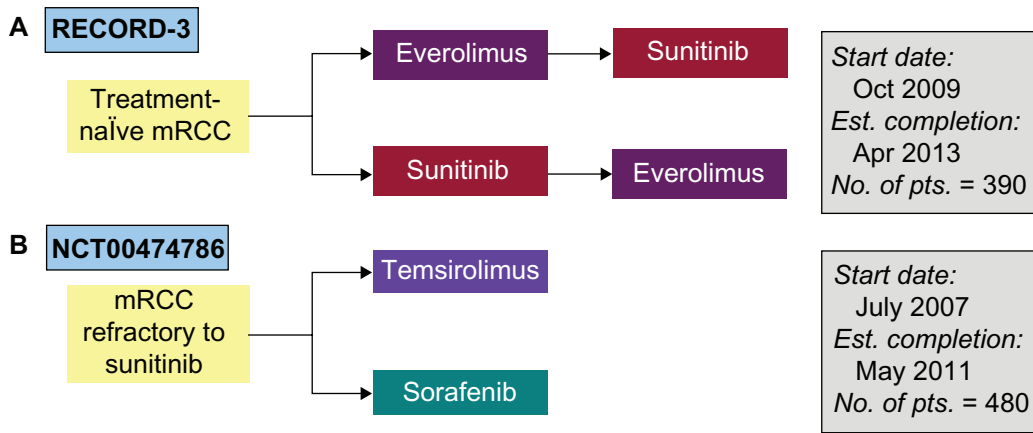


Figure 2. Ongoing clinical trials evaluating the optimal sequence of mTOR inhibitors.

Mechanisms of Resistance to mTOR Inhibition

While mTOR inhibitors show substantial clinical benefit in general, the agents appear to be primarily cytostatic. In most cases, disease progression will inevitably occur. As such, it will be critical for the scientific community to focus efforts on determining mechanisms of resistance to mTOR inhibition such that successful secondary strategies can be implemented. Mutations in the genes encoding mTOR itself have been

shown to induce a relative resistance to rapamycin.^{68,69} Furthermore, mutation of downstream targets of the mTOR complex (i.e. S6K1) can have a similar effect.⁷⁰ Somewhat paradoxically, activation of upstream moieties such as Akt may induce a relative sensitivity to mTOR inhibitors—this has been observed in panels of brain, prostate and breast cancer cells exposed to temsirolimus.^{71,72} Moving forward, it will be interesting to observe the clinical effect of a combined approach with Akt and mTOR inhibition. Akt inhibitors appear to

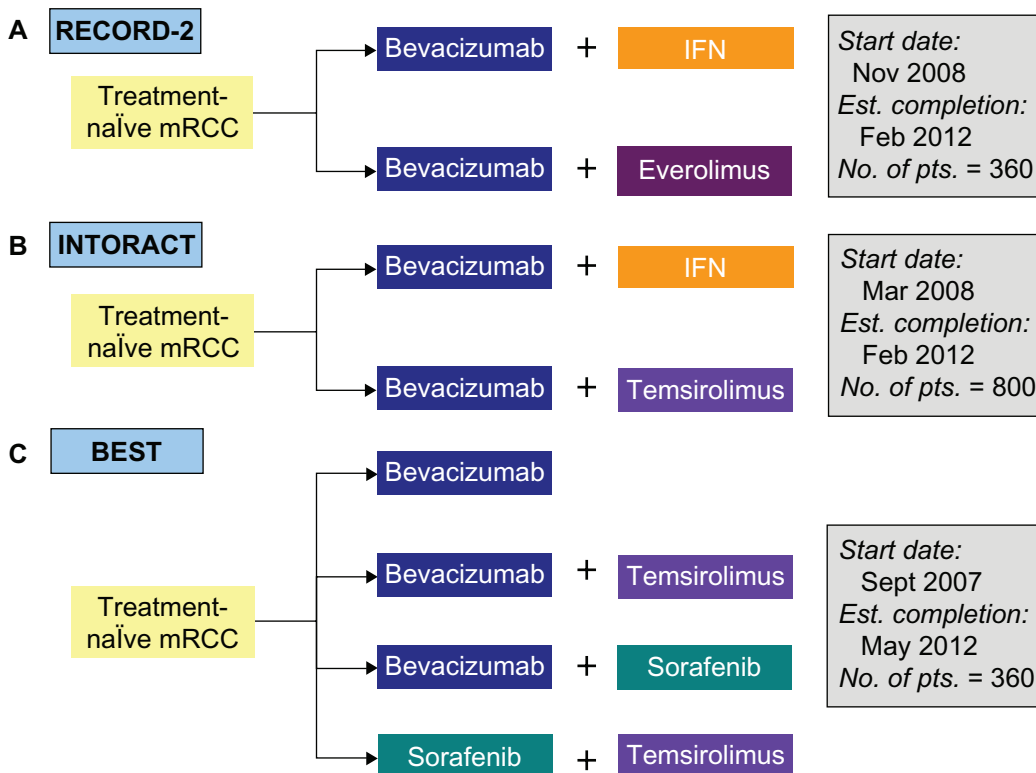


Figure 3. Ongoing clinical trials evaluating optimal combinations of mTOR inhibitors with VEGFR-directed therapy.



show moderate efficacy in the setting of mRCC; most notably, substantial phase II data has accumulated for the agent perifosine.^{73,74} A phase I study of perifosine in combination with temsirolimus is currently ongoing.⁷⁵

Conclusions

A multitude of clinical studies preceded the phase III trials leading to the approvals of temsirolimus and everolimus for mRCC. Each agent has ultimately found a unique application—temsirolimus in the treatment-naïve patient with poor-risk disease, and everolimus in the patient refractory to sunitinib and/or sorafenib. This is an important distinction from the VEGFR-directed therapies. In current algorithms, considerable overlap exists in the suggested use of sunitinib, bevacizumab and pazopanib, leaving the clinician in a state of clinical equipoise. The ongoing studies of mTOR inhibitors (including INTORACT, RECORD-2 and RECORD-3) may aid in further defining the optimal sequence and synergy with other targeted agents. While these comparative designs may refine existing algorithms, a fundamental goal that remains is personalization of cancer treatment. The identification of biomarkers to predict response to therapy is critical in this process. As a preeminent example of this work, Gordan et al have reported a unique classification of clear cell RCC tumors based on *VHL* gene status and consequent production of hypoxia-inducible factor (HIF).⁷⁶ Three distinct subtypes exist in this schema: (1) wild type (WT; *VHL* wild type), (2) H1H2 (*VHL* mutant with overexpression of HIF-1 α and HIF-2 α), and (3) H2 (*VHL* mutant with overexpression of HIF-2 α only). In gene expression studies, tumors characterized as either WT or H1H2 (representing ~70% of the specimens assessed) had enhanced Akt/mTOR signalling; in contrast, those characterized as H2 (the remainder) had increased c-myc signalling. Further prospective efforts may therefore be aimed at determining if WT and H1H2 tumors are particularly sensitive to mTOR inhibitors. Use of biomarker-based strategies to personalize care may ultimately yield the most effective clinical application of mTOR inhibitors.

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