The Oncologist®

Academia–Pharma Intersect: Genitourinary Cancer

Everolimus (RAD001) in the Treatment of Advanced Renal Cell Carcinoma: A Review

SANJIV S. AGARWALA,[a] SCOTT CASE[b]

[a]St. Luke's Cancer Center, Bethlehem, Pennsylvania, USA; [b]SciStrategy Communications, West Conshohocken, Pennsylvania, USA

Key Words. Everolimus • mTOR protein • Carcinoma • Renal cell • Receptors • Vascular endothelial growth factor • Receptor protein tyrosine kinases • Inhibitors • Angiogenesis • Targeted therapy

Disclosures: Sanjiv S. Agarwala: *Honoraria:* Wyeth, Novartis, Schering Plough; **Scott Case:** None.

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ABSTRACT

Historically, there have been few treatment options for patients with advanced renal cell carcinoma (RCC) besides immunotherapy with interleukin-2 and interferon (IFN)-α. Targeted therapies have improved clinical outcomes over the past several years. These include the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors sunitinib and sorafenib, which inhibit angiogenic signaling in endothelial cells and vascular pericytes predominantly through VEGFR and platelet-derived growth factor receptor β. Also included is the anti-VEGF monoclonal antibody bevacizumab used in combination with IFN-α. These agents mediate their antitumor effects by interfering with the VEGF signaling pathway, thereby inhibiting angiogenesis and causing tumor shrinkage. However, ultimately, most patients develop resistance and experience disease progression during VEGF/VEGFR-targeted therapy, and until the recent approval of the mammalian target of rapamycin (mTOR) inhibitor everolimus (RAD001), there were no agents available with proven activity in this setting. This review describes the clinical development of everolimus in advanced RCC and the rationale for the use of mTOR inhibitors after failure of VEGF/VEGFR inhibitors. ***The Oncologist*** 2010;15:236–245

INTRODUCTION

In most clear cell renal cell carcinoma (RCC) cases, loss of the ability to downregulate cellular responses to hypoxic stress drives angiogenesis and the progressive growth of the tumor. Normally, the von Hippel-Lindau gene product VHL participates in an oxygen-dependent process to target the transcription factor hypoxia-inducible factor (HIF)-1α for proteasomal degradation. Under conditions of hypoxic stress, HIF-1α migrates to the nucleus, where it forms a transcription factor for the production of angiogenic growth factors and the many other proteins involved in the cellular hypoxic response. In normoxia, VHL prevents this stimulation by removing HIF-1α before it enters the nucleus. In clear cell RCC, cells have lost the ability to produce VHL and the ability to downregulate the hypoxic response [1].

The new therapies that have entered the clinic over the

Correspondence: Sanjiv S. Agarwala, M.D., Oncology & Hematology, St. Luke's Cancer Center, 801 Ostrum Street, Bethlehem, Pennsylvania 18015, USA. Telephone: 610-954-2145; Fax: 610-954-2108; e-mail: AgarwaS@slhn.org Received July 7, 2009; accepted for publication February 10, 2010; first published online in ***The Oncologist*** *Express* on March 9, 2010; available online without subscription through the open access option. 1083-7159/2010/$30.00/0 doi: 10.1634/theoncologist.2009-0141

past few years, specifically sorafenib and sunitinib, attack the angiogenic response in RCC by inhibiting the ability of endothelial cells to respond to the overproduction of the angiogenic growth factors vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Sorafenib and sunitinib are low-molecular-weight competitive inhibitors of the tyrosine kinase activity of the receptors for VEGF and PDGF present on the surface of endothelial cells. Both sunitinib and sorafenib also inhibit other cellular kinases and may have direct effects on tumor growth, but their activity is primarily directed at endothelial cells. Bevacizumab, also approved for use in RCC, is a monoclonal antibody that binds VEGF, preventing the agent's interaction with its receptor on endothelial cells. These antiangiogenic agents demonstrate better efficacy than with cytokine therapies and likely extend the life of most patients. Recent data suggest that their use in an optimum sequence may prolong the median survival time from initial diagnosis of metastatic disease to >2 years. However, as information on longer treatment with these agents becomes available, it is increasingly apparent that these agents sometimes have significant toxicities [2, 3] and that, as with nearly all cancer therapies, they are not curative: patients eventually relapse and succumb, and the need for additional drug development continues.

In tumor cells, endothelial cells, and other cells of the tumor milieu, the synthesis of key proteins for cell growth, cell division, and angiogenesis is controlled by the mammalian target of rapamycin (mTOR) kinase. mTOR functions as a central controller, integrating signals from growth factor receptors with levels of nutrients and energy to determine whether the cell has the resources to support continued cell growth and cell division. In many cancers, including RCC, defects in pathways that signal through mTOR (Fig. 1) [4], including angiogenic growth factor signaling, drive mTOR and the resulting tumor growth. The mTOR inhibitors temsirolimus and everolimus inhibit inappropriate mTOR signaling and have been approved for the treatment of RCC. Everolimus is specifically approved for use after failure of VEGFR tyrosine kinase inhibitors (sorafenib, sunitinib). This article reviews the development of these agents and the optimization of their use in RCC with emphasis on the newly approved agent, everolimus (Afinitor®; Novartis Pharmaceuticals, Inc., East Hanover, NJ).

VEGF/VEGFR Inhibitors

Table 1 shows efficacy results from the pivotal trials of targeted therapies. The agents were evaluated in patients with metastatic RCC but in somewhat different populations; direct comparisons are not valid, and none of the agents have been directly compared in a single study.

Sorafenib

Sorafenib (Nexavar®; Bayer Pharmaceuticals Corporation, Wayne, NJ) inhibits the tyrosine kinase activity of the cell surface VEGF receptors (VEGFR-1, VEGFR-2, and VEGFR-3), PDGFR-β, Fms-like tyrosine kinase 3 (Flt-3), and stem cell factor receptor (c-Kit), and the intracellular serine/threonine Raf kinases [5]. In its pivotal 903-patient phase III trial, the preplanned interim analysis showed a significantly longer progression-free survival (PFS) interval with sorafenib than with placebo (5.5 months versus 2.8 months; hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.35–0.95; $p < .001$) in patients who had advanced clear cell RCC that had progressed after one systemic cytokine therapy regimen and were classified as good or intermediate risk on the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic survival scale for patients with RCC (MSKCC risk score) [6]. Tumor responses were seen in 10%, and 74% had stable disease (SD) for >28 days (compared with 2% with partial responses [PRs] and 53% with SD in the placebo group; $p < .001$). After a median of 23 weeks of treatment, common adverse events (AEs) of any grade with sorafenib (≥30% of patients) included diarrhea, rash, fatigue, and hand–foot syndrome (HFS). Grade 3 or 4 hypophosphatemia, elevated lipase, and HFS occurred in 13%, 12%, and 6% of these patients, respectively. Dose interruptions in 21% of the sorafenib-treated patients were principally a result of HFS and diarrhea. Rare (1%–2%) serious adverse events (SAEs) included hypertension, dyspnea, and cardiac ischemia [7]. After the preplanned analysis, patients in the placebo arm were allowed to cross over to treatment with sorafenib. At the final data cutoff 16 months after crossover, the survival time in the sorafenib-treated cohort was 17.8 months, compared with 15.2 months for the placebo group (HR, 0.88; 95% CI, 0.74–1.04; $p = .146$). After censoring of the crossover patients, the estimated overall survival (OS) duration for the placebo-treated patients was only 14.3 months (HR, 0.78; CI, 0.62–0.97; $p = .0287$) [3]. In December 2005, the U.S. Food and Drug Administration (FDA) granted approval for the use of sorafenib in patients with advanced RCC; sorafenib was later approved by the European Medicines Agency (EMEA) (July 2006) for use in patients who have advanced RCC after failure of cytokine-based therapy or who are considered unsuitable for such therapy.

Sunitinib

Sunitinib (Sutent®; Pfizer Inc., New York) received U.S. regulatory approval for use in advanced RCC in January

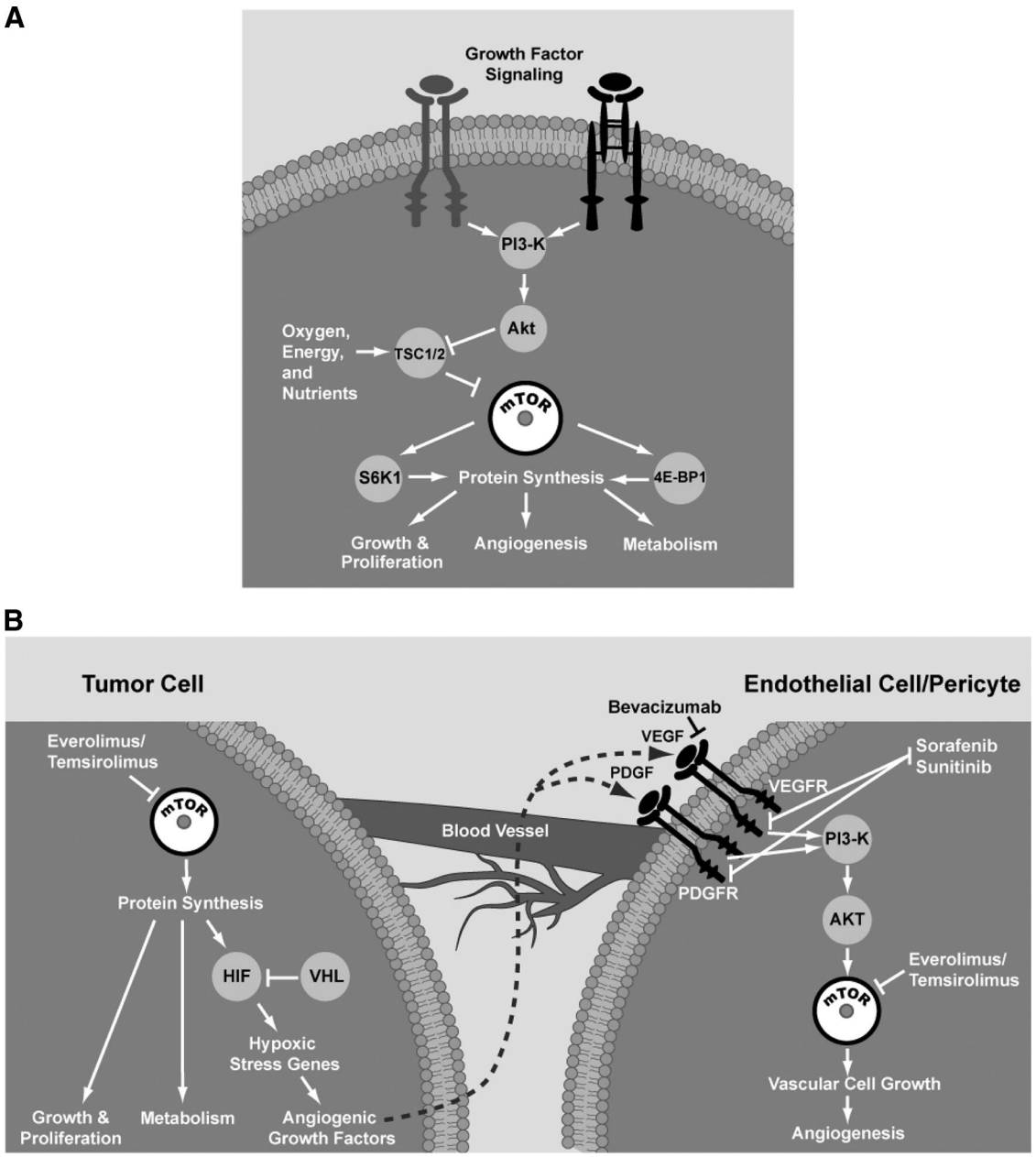

Figure 1. PI3K/Akt/mTOR pathway signaling in tumor and vascular endothelial cells. The PI3K/Akt/mTOR pathway **(A)** and molecular targets for treatment in renal cell carcinoma **(B)**.

Abbreviations: 4E-BP1, eukaryotic initiation factor 4E binding protein 1; HIF, hypoxia-inducible factor; mTOR, mammalian target of rapamycin; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PI3K, phosphatidylinositol 3-kinase; S6K1, S6 kinase 1; TSC, tuberous sclerosis complex; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; VHL, von Hippel-Lindau.

2006 and EMEA approval in July of the same year. Sunitinib principally inhibits the tyrosine kinase activity of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, c-Kit, Flt-3, and RET, and to a lesser extent the activity of several other kinases [5]. In its pivotal phase III trial, sunitinib was compared with interferon IFN-α in the first-line treatment of 750 patients with mostly good- and intermediate-risk metastatic RCC, and was found to result in a significantly longer PFS interval (11 months versus 5 months; HR, 0.42; 95% CI, 0.32–0.54; $p < .001$) [8]. Objective responses (PRs) occurred in 31% of patients treated with sunitinib, compared with 6% of patients treated with IFN-α ($p < .001$). Treatment-related AEs occurred more frequently with sunitinib than with IFN-α. After a median of 6 months of treatment, common AEs of any grade during treatment with sunitinib (≥30% of patients) included diar-

Table 1. Phase III trials in patients with advanced RCC

Study	Agents	Line	Patients	PFS (mos)	OS (mos)	ORR (%)
Motzer et al. [8]	Sunitinib	First line	All risk groups	11.0	26.4	31
	IFN-α			5.0	21.85	6
				HR, 0.42; $p < .001$	HR, 0.82; $p = .051$	$p < .001$
Escudier et al. [12]	Bevacizumab + IFN-α	First line	All risk groups	10.2	23.3	31
	IFN-α			5.4	21.3	13
				HR, 0.63; $p = .0001$	HR, 0.86; $p = .129$	$p = .0001$
Rini et al. [14]	Bevacizumab + IFN-α	First line	All risk groups	8.5	18.3	25.5
	Placebo			5.2	17.4	13.1
				HR, 0.71; $p < .0001$	HR, 0.86; $p = .069$	$p < .0001$
Hudes et al. [27]	Temsirolimus	First line	Intermediate and poor risk	3.1	10.9	8.6
	IFN-α			5.5	7.3	4.8
				NR	HR, 0.73; $p = .008$	NR
Escudier et al. [7]	Sorafenib	Second line	Good and intermediate risk	5.5	17.8	10
	Placebo			3.1	15.2	2
				HR, 0.44; $p < .001$	HR, 0.88; $p = .146$	$p < .001$
Motzer et al. [36]	Everolimus	Second line	All risk groups, VEGFR TKI failure	4.0	NR	1
	Placebo			1.9	NR	0
				HR, .30; $p < .0001$		NR

Abbreviations: HR, hazard ratio; IFN-α, interferon α; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

rhea, fatigue, and nausea. Left ventricular ejection fraction declined in 10% of patients (3% of those treated with IFN-α), but grade 3 decreases were rare (2%). Grade 3 or 4 events with sunitinib ($\geq$7% of patients) included increased lipase (13%), lymphopenia (12%), neutropenia (11%), hypertension (8%), thrombocytopenia (8%), and fatigue (7%). Among the sunitinib-treated patients, 38% had dose interruptions resulting from AEs [8].

In the final analysis, the median OS time with sunitinib (26.4 months) was longer than that with IFN-α (21.8 months) (HR, 0.821; 95% CI, 0.673–1.001; $p = .051$) [2]. Sunitinib is occasionally associated with prolongation of the QT interval on electrocardiography. It is recommended that sunitinib not be used in patients with congestive heart failure and be used with caution in patients who have had cardiac events within 12 months of initiating therapy. Hypothyroidism increases with the length of exposure to sunitinib [9], and it is of interest that sunitinib is being studied in patients with thyroid cancer.

Pazopanib

Pazopanib (Votrient™; GlaxoSmithKline, London, UK) is a selective inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, c-Kit, PDGFR-α and PDGFR-β. It was tested in comparison with placebo in a randomized phase III study in 233 treatment-naïve and 202 cytokine-pretreated patients with advanced RCC. In a preliminary report from that study, the median PFS interval in treatment-naïve patients was 11.1 months with pazopanib, compared with 2.8 months with placebo (HR, 0.40; 95% CI, 0.27–0.60; $p < .0000001$). In the cytokine-pretreated patients, the PFS intervals were 7.4 months with pazopanib and 4.2 months with placebo (HR, 0.54; 95% CI, 0.35–0.84; $p < .001$). These results are comparable with those seen with sorafenib and sunitinib in similar groups of patients [10].

Bevacizumab

Bevacizumab (Avastin®; Genentech Inc., South San Francisco, CA) is a humanized monoclonal antibody against VEGF-A that prevents VEGF-A stimulation of its receptor (VEGFR-2) on endothelial cells. Bevacizumab is approved in Europe (2007) and the U.S. (2009) for use with IFN-α in patients with previously untreated metastatic RCC. Two phase III trials compared IFN-α plus bevacizumab with IFN-α alone in previously untreated patients with metastatic RCC and predominantly favorable and intermediate MSKCC risk scores [11]. The Avastin and Roferon in Renal Cell Carcinoma (AVOREN) trial, conducted mainly in Europe, compared bevacizumab plus IFN-α with placebo plus IFN-α in 649 patients and showed that bevacizumab treatment led to a significantly longer PFS interval (10.2 months, versus 5.4 months; HR, 0.63; $p = .0001$) [12]. The overall response rate (ORR) in the bevacizumab plus IFN-α group was 31%, versus 13% in the placebo plus IFN-α group ($p = .0001$), with SD in 46% of patients. After a median of 9.7 months of treatment, common treatment-related AEs of any grade (≥30% of patients) included pyrexia, anorexia, bleeding, fatigue, and asthenia. Frequent grade 3 or 4 toxicities (>7% of patients) included fatigue (12%), asthenia (10%), and proteinuria (7%). In the final data analysis, the median survival times were 23.3 months in the bevacizumab arm and 21.3 months in the placebo arm (HR, 0.86; 95% CI, 0.72–1.04; $p = .1291$) [13].

The trial conducted in the U.S. (Cancer and Leukemia Group B [CALGB] 90206) compared bevacizumab plus IFN-α (same doses as in the AVOREN study) with IFN-α monotherapy in 732 patients. The PFS interval with bevacizumab plus IFN-α was 8.5 months, compared with 5.2 months with IFN-α alone (HR, 0.71; 95% CI, 0.61–0.83; $p < .0001$). There was also a higher ORR with bevacizumab plus IFN-α (25.5%) than with IFN-α monotherapy (13.1%; $p < .0001$). The difference in the PFS time and ORR between the two trials may reflect a worse risk–group distribution of treated patients, the absence of nephrectomy in the majority of patients, and the possibility of a lower proportion of tumors of strictly clear cell histology in the CALGB trial. Frequent grade 3 or 4 toxicities (≥7% of patients) in the bevacizumab plus IFN-α group included fatigue (35%), anorexia (17%), proteinuria (15%), and hypertension (9%) [14].

Unfortunately, neither trial included a bevacizumab only arm, so the relative contribution of IFN-α to the regimen remains an open question.

Sorafenib, sunitinib, and bevacizumab plus IFN-α have substantially improved on the 6.5%–7.5% response rate and about doubled the 12- to 13-month OS time historically achieved with interleukin (IL)-2 or IFN-α cytokine therapy in patients with advanced RCC [15]. Studies have shown that, somewhat contrary to the expectation of common mechanisms of resistance [16], sorafenib and sunitinib do not appear to be entirely crossresistant. Patients whose tumors progress on either sorafenib or sunitinib may benefit from subsequent treatment with the other agent [17–21]. In studies in which patients began therapy with sorafenib or sunitinib and were switched to the other agent at progression, the median OS time was 24–30 months, approximately the same OS time seen with first-line sunitinib or bevacizumab plus IFN-α [18, 21]. Although this is encouraging, it is reasonable to expect that expanding the antitumor effects beyond VEGF/VEGFR inhibition may produce more encouraging results.

The mTOR inhibitors are also approved for the treatment of patients with advanced RCC. Everolimus and temsirolimus have direct antitumor effects through inhibition of the protein synthesis required for tumor cell growth and proliferation, they directly inhibit angiogenesis through the same effects on endothelial cells and other cells involved in neovascularization (pericytes), and they have indirect effects in inhibiting the synthesis of the growth factors that tumor cells require for their own growth and angiogenesis (VEGF, PDGF, fibroblast growth factor [FGF], transforming growth factor-α) [22, 23]. Because the antitumor mechanisms of these agents complement and extend those of sorafenib, sunitinib, and bevacizumab with little overlap in their safety profiles, sequential or combination therapy with these agents is being investigated as a rational option to be used early in the sequence of treatments for metastatic RCC.

mTOR and mTOR Inhibitors

The mTOR kinase integrates signals relating to energy, nutrients, and oxygen to determine whether the cell has the resources to grow and divide in response to growth factor stimulation (Fig. 1A). Positive signals allow mTOR to act on its targets S6 kinase 1 (S6K1), which activates the ribosomal S6 protein and ribosomal synthesis, and eukaryotic translation initiation factor 4E binding protein (4E-BP1), which when activated allows transcription of the proteins involved in the regulation of cell growth, cell cycle progression, and cellular metabolism. Through the synthesis of HIF-1, mTOR controls the production of proteins involved in angiogenesis (e.g., VEGF) and other responses that increase supplies of nutrients and energy for growing cells [24, 25]. mTOR is highly conserved from fungi to mammals, and mutations in *mTOR* are lethal very early in development, which is particularly significant in that the signaling pathways that converge on mTOR are themselves dysregulated in most cancer cells [4]. Defects in the signal-

ing components upstream of mTOR, including tumor suppressor genes, oncogenes, and growth factor receptors, may be required events in tumorigenesis [22]. Inappropriate activation of the mTOR signaling pathway in the pathogenesis of cancer often correlates with a more aggressive tumor and a worse prognosis [4].

Rapamycin and its analogs form an intracellular complex with a 12-kDa cytosolic protein, FKBP12 (FK506 binding protein), that inhibits mTOR activity and prevents activation of S6K1, which, in addition to activating the ribosomal S6 protein, has a negative feedback effect on Akt/protein kinase B (Akt). Consequently, mTOR inhibition enhances Akt activity, with the potential to promote cancer cell survival and chemoresistance. However, although the effect of Akt activation by mTOR inhibitors is an area of research interest, it has not been shown to affect clinical responses and it is not yet clear whether it is a common mechanism or limited to certain types of cells or certain physiologic conditions. It has been suggested that prolonged exposure to mTOR inhibitors may decrease Akt activity through effects on TORC2, the rapamycin-*insensitive* mTOR complex [26].

mTOR inhibitors are being investigated as anticancer agents based on their capacity to act directly on tumor cells by inhibiting tumor cell growth and proliferation, as well as for their ability to inhibit angiogenic activity by both direct effects on vascular cell proliferation and indirect effects on growth factor production (Fig. 1B).

Temsirolimus

Temsirolimus, a prodrug converted in vivo to rapamycin, was formulated for i.v. administration. It was evaluated in a phase III trial with randomization to temsirolimus (25 mg weekly), IFN-α (3–18 MU 3 times a week [tiw]), or a combination of 15 mg weekly temsirolimus and a reduced dose of IFN-α (3–6 MU tiw). The trial enrolled 626 previously untreated patients, 80% with metastatic clear cell RCC and 74% in the MSKCC poor-risk category [11]. Treatment with temsirolimus led to a significantly longer OS time than with IFN-α alone (10.9 months versus 7.3 months; HR, 0.73; $p = .008$), and the PFS interval was 5.5 months with temsirolimus, versus 3.1 months with IFN-α. The ORR was 8.6%, and SD for ≥6 months was seen in 23.5% of patients. Common treatment-related AEs of any grade (≥30% of patients) included asthenia, rash, anemia, nausea, and anorexia. Frequent grade 3 or 4 toxicities (≥7% of patients) included anemia (20%), asthenia (11%), hyperglycemia (11%), and dyspnea (9%) [27]. Further analysis identified noninfectious pneumonitis/interstitial lung disease as a potential SAE [28].

In May 2007, temsirolimus received U.S. regulatory approval for metastatic RCC, and it was approved by the EMEA in November 2007 for use limited to the first-line treatment of poor-risk patients. A subgroup analysis of the phase III data [29] presented at the 2007 meeting of the American Society of Clinical Oncology suggested that temsirolimus may be as effective against non–clear cell RCC (HR, 0.55; 95% CI, 0.33–0.90) as against clear cell RCC (HR, 0.85; 95% CI, 0.67–1.08), but the number of non–clear cell patients was too small to draw definitive conclusions. Although this observation may actually reflect the limited activity of IFN-α in non–clear cell RCC, it could also indicate that mTOR inhibitors have activity in a broader group of RCC patients in whom tumor growth is driven by mechanisms other than *VHL* mutations. This question is currently being addressed in clinical trials.

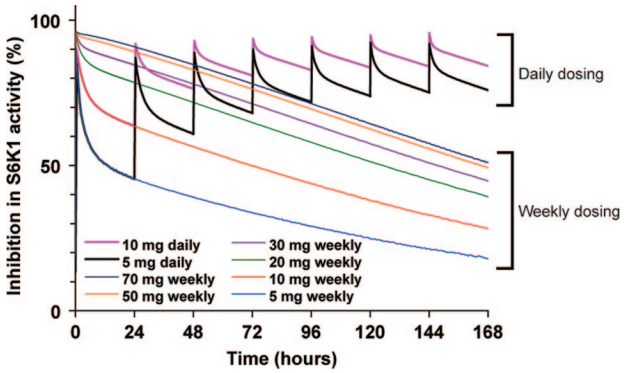

Figure 2. Consistent sustained inhibition of S6 kinase 1 (S6K1) by everolimus with daily versus weekly dosing.

From Tanaka C, O'Reilly T, Kovarik JM et al. Identifying optimal biologic doses of everolimus (RAD001) in patients with cancer based on the modeling of preclinical and clinical pharmacokinetic and pharmacodynamic data. J Clin Oncol 2008;26:1596–1602. Reprinted with permission from the American Society of Clinical Oncology. All rights reserved.

Everolimus

Everolimus has been formulated for oral administration with a dosing strategy developed in phase I clinical trials [30]. Everolimus is a derivative of rapamycin and is not converted to rapamycin in vivo. Everolimus has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and has obtained marketing authorization (Certican®; Novartis Pharmaceuticals, Inc., East Hanover, NJ) for prophylaxis of rejection in renal and cardiac transplantation in Europe.

Everolimus Phase I Clinical Development

Phase I studies determined the optimum dose and regimen of everolimus used in subsequent trials. Phase I clinical studies and preclinical–clinical pharmacokinetic–pharmacodynamic modeling [31, 32] predicted that a 5- to 10-mg

daily dose would result in greater inhibition (extent and duration) of mTOR and its downstream targets than would the same dose on a weekly schedule (Fig. 2) [32]. Subsequent studies confirmed that 10 mg/day was the optimum daily dose for phase II monotherapy studies with everolimus [22]. Phase I studies also assessed the effects of everolimus on mTOR activity in tumors from treated patients and confirmed that daily dosing resulted in profound and sustained inhibition of mTOR activity in tumor tissue [33]. The 30-hour half-life of everolimus is compatible with daily dosing, and 5–10 mg/day sustains the circulating concentration (trough) of everolimus above the minimum effective concentration and minimizes drug peaks that could potentially exacerbate toxicity. Of note, the advantage of continuous dosing over an intermittent regimen is also being investigated with sunitinib in RCC patients to avoid the treatment breaks with the 4-weeks-on-2-weeks-off regimen, to possibly reduce toxicity, and to allow combination with other agents [34].

Clinical Activity of Everolimus in RCC

In phase I studies, 147 patients with advanced solid tumors refractory to standard therapy were treated with everolimus either as single weekly (20 mg, 50 mg, and 70 mg) or continuous daily (5 mg and 10 mg) oral doses until progression [31, 33]. Among the 147 patients, 12 had metastatic RCC (8.2% of the total study population). One RCC patient had a PR (8.3%), six were progression free at 6 months (50%), and four were progression for >12 months (33.3%).

A phase II study to assess the safety and efficacy of 10 mg/day oral everolimus in 41 mostly pretreated patients with advanced clear cell RCC was started in 2005, before the approval of sorafenib and sunitinib. There was no limitation based on MSKCC risk score, and 83% of the patients had received prior therapy, with 61% having received cytokine therapy with IL-2 and/or IFN-α [35]. Fifty-seven percent of patients remained progression free for ≥6 months, with a median PFS interval of 11.2 months and a median OS time of 22.1 months. The ORR was 14% (all PRs), and 73% of patients had SD for ≥3 months. Overall, 70% of patients had either a response or SD for ≥6 months. This small phase II study supported the efficacy of everolimus in patients previously treated with cytokine therapy. Common treatment-related AEs (≥30% of patients) were anorexia, nausea, diarrhea, stomatitis, and pneumonitis. Grade 3 pneumonitis (18%) resulted in dose delays of 7–14 days and a dose reduction for seven patients, four of whom were successfully re-escalated to 10 mg/day. Grade 3 biochemical abnormalities included alanine aminotransferase elevation (10%), alkaline phosphatase elevation (8%), hyperglycemia (8%), and thrombocytopenia (8%).

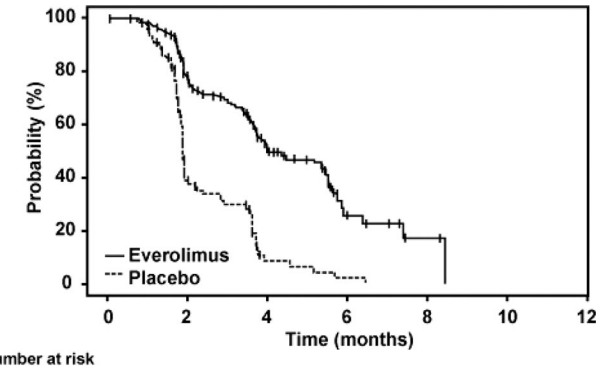

Figure 3. Kaplan–Meier estimates of progression-free survival.

From Motzer RJ, Escudier B, Oudard S et al. Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase III trial. Lancet 2008; 372:449–456. Reprinted with permission from Elsevier.

The encouraging phase II results led to the design of a pivotal phase III investigation of oral everolimus in patients with advanced RCC progressing after failure of treatment with sunitinib and/or sorafenib (Renal Cell Carcinoma Treatment with Oral RAD001 Given Orally, RECORD-1). When that trial began, sunitinib and sorafenib were both first-line treatment options for metastatic RCC, and this was the first randomized study to assess an mTOR inhibitor in this patient population [36]. Four hundred ten patients with clear cell RCC that had progressed within 6 months of stopping treatment with sorafenib, sunitinib, or both drugs were randomly assigned in a 2:1 ratio to receive everolimus, 10 mg once daily ($n = 272$), or placebo ($n = 138$) in conjunction with best supportive care. Everolimus treatment resulted in a significantly longer median PFS interval than with placebo (4.0 months versus 1.9 months; HR, 0.30; 95% CI, 0.22–0.40; $p < .0001$) in patients with progression after VEGFR tyrosine kinase inhibitor therapy (Fig. 3). There was no difference based on prior therapy or MSKCC risk score, and clinical benefit was maintained across all subgroups [36]. In an updated data analysis performed 8 months later, the median PFS time with everolimus was 4.9 months, versus 1.9 months in the placebo-treated patients (HR, 0.33; 95% CI, 0.25–0.43; $p < .001$), and 69% of the 277 everolimus-treated patients had either responded (2%) or had SD for ≥2 months [37]. Everolimus had a positive effect on patient survival (HR, 0.87; 95% CI, 0.65–1.15; $p = .162$) despite the crossover design, and when crossover patients were censored from the analysis, the estimated median survival time of the everolimus-treated patients was 14.8 months, compared with 10.0 months for those treated with placebo [38].

The safety profile of everolimus in this pretreated pop-

Table 2. Treatment-related adverse events associated with everolimus

	Everolimus group ($n = 269$)			Placebo group ($n = 135$)		
Adverse event	**All grades**	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Stomatitis[a,b]	107 (40%)	9 (3%)	0	11 (8%)	0	0
Rash	66 (25%)	2 (<1%)	0	6 (4%)	0	0
Fatigue	53 (20%)	8 (3%)	0	22 (16%)	1 (<1%)	0
Asthenia	48 (18%)	4 (1%)	0	11 (8%)	1 (<1%)	0
Diarrhea	46 (17%)	4 (1%)	0	4 (3%)	0	0
Anorexia	44 (16%)	1 (<1%)	0	8 (6%)	0	0
Nausea	41 (15%)	0	0	11 (8%)	0	0
Mucosal inflammation	39 (14%)	3 (1%)	0	3 (2%)	0	0
Vomiting	32 (12%)	0	0	5 (4%)	0	0
Cough	32 (12%)	0	0	5 (4%)	0	0
Dry skin	29 (11%)	1 (<1%)	0	5 (4%)	0	0
Infections[a,c]	27 (10%)	6 (2%)	3 (1%)	3 (2%)	0	0
Pneumonitis[d]	22 (8%)	8 (3%)	0	0	0	0
Dyspnea	22 (8%)	4 (1%)	0	3 (2%)	0	0
Laboratory abnormality						
Anemia	244 (91%)	24 (9%)	1 (< 1%)	103 (76%)	7 (5%)	0
Hypercholesterolemia[a]	205 (76%)	9 (3%)	0	43 (32%)	0	0
Hypertriglyceridemia	191 (71%)	2 (<1%)	0	41 (30%)	0	0
Hyperglycemia[a]	135 (50%)	31 (12%)	0	31 (23%)	2 (1%)	0
Raised creatinine	125 (46%)	1 (< 1%)	0	44 (33%)	0	0
Lymphopenia[a]	114 (42%)	38 (14%)	4 (1%)	39 (29%)	7 (5%)	0
Raised alkaline phosphatase	101 (37%)	2 (<1%)	0	40 (30%)	2 (1%)	0
Hypophosphatemia[a]	87 (32%)	12 (4%)	0	9 (7%)	0	0
Leukopenia	70 (26%)	0	0	11 (8%)	0	1 (<1%)
Raised aspartate aminotransferase	56 (21%)	1 (<1%)	0	9 (7%)	0	0
Thrombocytopenia	55 (20%)	2 (<1%)	0	3 (2%)	0	1 (<1%)
Raised alanine aminotransferase	48 (18%)	1 (<1%)	0	5 (4%)	0	0
Hypocalcemia	46 (17%)	0	0	8 (6%)	0	0
Neutropenia	29 (11%)	0	0	4 (3%)	0	0

[a]Sum of grade 3 and 4 events significantly different between everolimus group and placebo group (two-sided Fisher's exact test): stomatitis, $p = .03$; infections, $p = .03$; hypercholesterolemia, $p = .03$; hyperglycemia, $p < .0001$; lymphopenia, $p = .002$; hypophosphatemia, $p = .01$. No adaption for multiple testing was done.
[b]Includes aphthous stomatitis, mouth ulceration, and stomatitis.
[c]Includes all infections.
[d]Includes interstitial lung disease, lung infiltration, pneumonitis, pulmonary alveolar hemorrhage, and pulmonary toxicity.
From Motzer RJ, Escudier B, Oudard S et al. Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449–456. Reprinted with permission from Elsevier.

ulation was good (Table 2). Nonhematologic AEs of any grade included stomatitis (40%), rash (25%), and fatigue (20%). Frequent grade 3 or 4 toxicities included stomatitis (3%), infections (grade 3, 2%; grade 4, 1%), and noninfectious pneumonitis (3%). Grade 3 or 4 laboratory abnormalities (≥1% of patients) included lymphopenia (grade 3, 14%; grade 4, 1%), hyperglycemia (12%), hypophosphatemia (4%), and hypercholesterolemia (3%) [36]. Noninfectious pneumonitis is a toxicity associated with mTOR inhibition. It is a nonmalignant infiltration in the lungs, evident radiologically, usually nonsymptomatic (grade 1) or associated with minimal symptoms (grade 2), and reversible with drug discontinuation. Patients receiving mTOR inhibitors should be monitored for development of pneumonitis, and those with evidence of disease should have their dose reduced or stopped until recovery to grade ≤1.

Corticosteroids may be used if needed for higher grades, provided the noninfectious origin is confirmed [28].

Everolimus has received FDA (March 2009) and EMEA (May 2009) approval for the treatment of patients with advanced RCC after failure of treatment with sunitinib or sorafenib. Based on the trial data, everolimus also received a category 1 recommendation by the National Comprehensive Cancer Network for the second-line treatment of patients with advanced RCC after failure of tyrosine kinase therapy [39].

PERSPECTIVES

With the availability of sunitinib, sorafenib, bevacizumab, temsirolimus, and everolimus for metastatic RCC, this disease has been transformed from one with too few options to one with many options and a critical need for more research. Sequential treatment with these agents after disease progression to overcome resistance has become the usual clinical practice, but a great amount of work is still needed to determine whether existing agents may work better in combination or whether one specific sequence of these agents is superior to another, as suggested in early trials [18, 21]. Another urgent question is the nature of the resistance to VEGF/VEGFR-targeted therapies. Proposed mechanisms have focused on enhanced angiogenic signaling. Suggestions supported by experimental studies include the upregulation of HIF-1α to enhance the hypoxic response by greatly increasing levels of VEGF and PDGF and other factors needed for cell proliferation, and the upregulation of alternate proangiogenic pathways through other cell surface receptors such as those for FGF, insulin-like growth factor, ephrins, and angiopoietins [16]. The basis of current research combining everolimus or temsirolimus with bevacizumab and exploring optimal sequencing of the mTOR inhibitors with sunitinib and sorafenib is twofold: the expectation of additional antitumor effects with mTOR inhibition, as well as complementary angiogenic activities [40], and the position of mTOR downstream in the signaling pathways from VEGFR and PDGFR and downstream in the proposed alternate angiogenic signaling pathways.

The coming years will be even more exciting for RCC, and it is hoped that ongoing clinical trials will clarify some of the issues related to potential combinations and new drugs that have shown promise in phase II studies.

ACKNOWLEDGMENTS

Scott S. Case, Ph.D., of SciStrategy Communications was supported by Novartis Pharmaceuticals.

AUTHOR CONTRIBUTIONS

Conception/Design: Sanjiv S. Agarwala, Scott Case
Administrative support: Scott Case
Collection and/or assembly of data: Scott Case
Data analysis and interpretation: Sanjiv S. Agarwala
Manuscript writing: Sanjiv S. Agarwala
Final approval of manuscript: Sanjiv S. Agarwala

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