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# Differentiating mTOR Inhibitors in Renal Cell Carcinoma

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## Abstract

PI3K/Akt/mTOR signalling is dysregulated in many cancers, including renal cell carcinoma (RCC), and activation of this pathway has been suggested to correlate with aggressive behavior and poor prognosis in RCC tumors. mTOR inhibition plays a principal role in the targeted treatment of many cancer types, including RCC. Although mTOR inhibitors share the same mechanism of action, differences in metabolism, formulation and dosing schedule underpin distinct PK/PD profiles such that they may be differentiated for use in a variety of treatment niches. Approved mTOR inhibitors temsirolimus and everolimus serve as important therapeutic options within the current RCC treatment paradigm, although their recommended applications differ in setting and patient population characteristics. Clinical practice guidelines recommend temsirolimus for use in treatment-naive patients with poor-prognosis metastatic RCC of any histology (predominant clear cell or non-clear cell histology). Everolimus provides a standard-of-care therapy for patients with metastatic RCC whose disease has progressed after previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy. As therapeutic failure impacts the vast majority of patients with RCC, sequencing strategies of available agents or simultaneous targeting of multiple members of the PI3K/Akt/mTOR pathway may provide additional clinical benefit. Various classes of agents targeting the PI3K/Akt/mTOR pathway are

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currently being investigated, including mTORC1/mTORC2 kinase domain inhibitors, mTOR/PI3K dual inhibitors, PI3K-selective inhibitors, and programmed cell death 6 modulators. Clinical trials of mTOR inhibitors in a variety of tumor types are ongoing, and the role of mTOR inhibitors continues to evolve across the RCC treatment landscape.

**Keywords**

mTOR inhibitors; renal cell carcinoma; temsirolimus; everolimus; treatment; PI3K/Akt/mTOR pathway

## Introduction

Renal cell carcinoma (RCC) is the most common form of kidney cancer, representing up to 85% of cases.[1] Patients often present with advanced disease; approximately 25–30% of patients have metastatic RCC (mRCC) at diagnosis.[2,3] Whereas previous systemic treatment options were limited to cytokine therapy and investigational agents, in current practice targeted therapies are considered a standard of care in the mRCC setting.

Based on results from pivotal phase III clinical trials, seven targeted agents have received approval from the US Food and Drug Administration for the treatment of patients with mRCC.[3–12] These include the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab in combination with interferon-α (IFN-α), the VEGF receptor-tyrosine kinase inhibitors (VEGFr-TKIs) sorafenib, sunitinib, pazopanib, and axitinib, and the mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus. In the first-line setting, current guidelines based on level 1 evidence recommend the use of sunitinib, bevacizumab plus IFN-α, and pazopanib in patients in the favorable or intermediate Memorial Sloan-Kettering Cancer Center (MSKCC) risk category[13] and temsirolimus among patients of poor MSKCC risk.[14–17] Unfortunately, patients ultimately become resistant to first-line agents and require further treatment. Second-line options include sorafenib, sunitinib and pazopanib for use in cytokine-refractory patients, and everolimus is a standard of care for patients who fail initial VEGFr-TKI therapy.

The focus of this review is to compare and contrast preclinical and clinical evidence supporting the use of mTOR inhibitors as class of agents in patients with mRCC.

## The role of mTOR in RCC

mTOR is an important component of the phosphoinositide 3-kinase (PI3K)/Akt signalling pathway that mediates eukaryotic cell growth and proliferation (Fig. 1).[18–20] PI3K/Akt/mTOR signalling is dysregulated in many cancers, including RCC,[21] and activation of this pathway has been suggested to correlate with aggressive behavior and poor prognosis in RCC tumors.[22] Hyperactivity of mTOR signalling can occur via a number of mechanisms, including overexpression or activation of growth factor receptors, activation of mutations in PI3K/Akt, or decreased expression of tuberous sclerosis tumor suppressor genes TSC1/2, PTEN or Von Hippel-Lindau (VHL) tumor suppressor genes.[18,23] Overproduction of growth factors such as VEGF in tumor cells in turn can result in activation of mTOR signalling in

neighboring endothelial cells, leading to increased angiogenesis.[23] mTOR also regulates the translation of mRNA for hypoxia inducible factors (HIF)-1α and HIF-2α, as well as p70S6 kinase (p70S6K) in cancer cells. Overexpression of HIF-1α and HIF-2α appears to be a critical step in the pathogenesis of RCC,[21] while overexpression of p70S6K is observed in ~60% of patients with RCC and seems to be predictive of response and treatment outcomes.[24,25]

mTOR is a serine/threonine kinase that specifically binds to and is inhibited by the FK506 binding protein 12 (FKBP12)-rapamycin complex, a complex involved in the regulation of protein translation, cell growth, and metabolism.[18,19,26] Subsequently, phosphorylation of downstream targets p70S6K and 4E binding protein (4E-BP1) is also inhibited.[21,27] Structurally mTOR exists as two distinct protein complexes, mTOR complex 1 (mTORC1) and complex 2 (mTORC2).[18,19,28] mTORC1 is involved in rapamycin-sensitive temporal control of cell growth and is activated by Akt via direct phosphorylation of TSC2 and by regulation of cellular energy. mTOR2 is involved in rapamycin-insensitive spatial control of cell growth. Inhibition of these protein complexes ultimately results in decreased cell growth and proliferation, cellular metabolism and angiogenesis, leading to cell cycle block at the G1 phase.[18] Dysregulation of mTOR signalling is apparent in many types of tumors; mTOR has presented itself as a valid target for the treatment of cancer in RCC.[19]

## Rapamycin and its analogs

The mTOR inhibitors temsirolimus, everolimus and ridaforolimus are structural derivatives of the macrocyclic lactone rapamycin (also known as sirolimus, Fig. 2). Originally shown to possess fungicidal, immunosuppressive and antiproliferative properties, sirolimus was first approved as an immunosuppressant for patients with solid organ transplants, followed by usage in sirolimus-eluting stents for the prevention of coronary artery restenosis.[29] Recent phase I and II trials have also shown sirolimus to reduce the size of angiomyolipomas in patients with tuberous sclerosis complex (TSC) and lymphangioleiomyomatosis (LAM).[30–32] Temsirolimus, everolimus and ridaforolimus inhibit mTOR by binding to the cytosolic protein FKBP-12. All three agents have been evaluated in clinical cancer trials.[21,29] Temsirolimus has been investigated as a treatment for advanced cancer, including mRCC, locally advanced or metastatic breast cancer and mantle cell lymphoma.[7,33–36] Everolimus has been assessed as a treatment for patients with advanced cancer, including pancreatic neuroendocrine tumors (pNET), metastatic breast cancer and mRCC.[10,21,29,37] Ridaforolimus is being evaluated in patients with advanced solid malignancies, including metastatic sarcoma and RCC.[38–40]

## Development of mTOR inhibitors as novel therapies for mRCC and other cancers

### Temsirolimus

In preclinical studies, temsirolimus exhibited antitumor activity (normalized p70S6K activity and reduced neoplastic proliferation) in a variety of cancers, including glioma, rhabdomyosarcoma, medulloblastoma and prostate and breast cancer.[41–45] Results from a

phase I study in patients with advanced solid tumors identified weekly temsirolimus IV 25, 75 and 250 mg/m$^2$ to be appropriate doses for further clinical testing.[46] Subsequent clinical studies demonstrated IV temsirolimus to have antitumor activity in patients with various types of cancer, including mRCC (Table 1).[7,33–36,46–51]

In a phase II study, patients with advanced-refractory RCC ($n$ = 111) treated with temsirolimus 25, 75 and 250 mg weekly IV displayed antitumor activity at all dosing levels and treatment was generally well tolerated.[33] Since no major differences in terms of toxicity or measurable efficacy between the three dosing levels were observed, a 25-mg weekly dosage was selected for further clinical evaluation. Specifically, when categorized by MSKCC criteria,[13] intermediate- and poor-risk patients demonstrated improved median survival compared with that predicted by the criteria, which were developed in IFN-α treated patients. A randomized phase III trial in treatment-naive patients with poor-prognosis mRCC demonstrated that temsirolimus 25 mg IV weekly prolonged progression-free survival (PFS) and overall survival (OS) compared with IFN-α (3.8 months *vs* 1.9 months for PFS; 10.9 months *vs* 7.3 months for OS, respectively).[7] Based on these results, IV temsirolimus was approved in 2007 as a targeted therapy for patients with advanced RCC in the United States, and exclusively as a first-line treatment for patients with poor prognosis in Europe.[52]

An oral formulation of temsirolimus was developed to improve dosing convenience. A phase I study determined the maximum tolerated dose (MTD) of oral temsirolimus in patients with advanced cancer, starting at a dose of 25 mg administered on an intermittent schedule.[53] Antitumor activity was observed at a MTD of 75 mg once daily for 5 days every 2 weeks. In a phase II study, patients with metastatic breast cancer (mBC) received oral temsirolimus (25 mg daily or intermittently using 75 mg for 5 days every 2 weeks), letrozole, or both. During the study, temsirolimus dose was amended to 10 mg daily or 30 mg intermittently, as 83% of patients required dose delays, reductions, or discontinuations. Overall, both modified doses combined with letrozole were tolerable and showed clinical activity.[54]

Following this, a randomized, placebo-controlled, phase III trial of intermittent oral temsirolimus 30 mg (daily for 5 days every 2 weeks) with 2.5 mg letrozole or letrozole alone was conducted in postmenopausal women with locally advanced or mBC.[51] However, the study was terminated early due to a lack of efficacy and a poorer tolerability profile for the combination regimen compared with letrozole alone. Although phase II results of the combination regimen were encouraging, negative findings in the phase III setting may have resulted from the inability to identify patients with PI3k/Akt/mTOR pathway-dependent tumors and inclusion of patients with ER-positive mBC.[55] Alternatively, intermittent dosing may not have been effective in inhibiting the PI3k/Akt/mTOR pathway. This in itself is interesting given the results of the phase III BOLERO-2 trial, in which everolimus plus exemestane improved PFS by 4.1 months over exemestane alone in patients with mBC who had progressed on letrozole.[56] Due to these negative phase III temsirolimus data and the apparent lack of interest in developing a clinical biomarker to track target activity such as 4E-BP1 or p70S6K,[42,57] development of an oral formulation of temsirolimus has stalled.

## Everolimus

The antitumor activity of oral everolimus was initially demonstrated in a rat pancreatic tumor model at dosages of 0.5 or 2.5 mg/kg daily and 5 mg/kg once or twice weekly.[58] A single dose of everolimus 5 mg/kg was shown to block phosphorylation of 4E-BP1 and inactivate S6K1 in human peripheral blood mononuclear cells (PBMCs).[58] Dosing in humans was evaluated in a phase I dose escalation study of patients with advanced cancer who received oral everolimus 5, 10, 20 and 30 mg weekly.[59] Everolimus 20 mg weekly dosing was determined to be the minimum dose to provide sustained mTOR inhibition over a 1-week period. Additionally, everolimus 50 and 70 mg weekly and 5 and 10 mg daily were also assessed and the higher dose further evaluated. Phase I PK/PD studies demonstrated that continuous daily dosing with everolimus 10 mg resulted in a more profound and sustained inhibition of mTOR than that achieved with a weekly dosage schedule.[60,61] Specifically, treatment with 10 mg daily or ≥50 mg weekly dosing of everolimus resulted in almost complete inhibition of S6K1 ($P < 0.001$) and eukaryotic initiation factor 4G (eIF-4G, $P < 0.001$). However, a correlation between everolimus plasma trough concentrations and inhibition of peIF4G and p4E-BP1 was not evident with weekly dosing, only daily dosing.[61] On that basis, a daily dose of 10 mg was selected for further trials with everolimus. The clinical benefit of oral everolimus was subsequently shown in patients with various cancers, including mRCC (Table 2).[10,37,56,62–76]

The antitumor activity of 10 mg daily everolimus was demonstrated in a phase II study conducted in patients with mRCC of predominantly clear-cell histology who had received ≤1 prior therapy other than an mTOR inhibitor.[65,77] Data from the pivotal phase III RECORD-1 study showed that among patients with clear-cell mRCC, everolimus 10 mg daily resulted in a median PFS of 4.9 months compared with 1.9 months with placebo and treatment was generally well tolerated.[10] Pharmacodynamic modelling of tumor growth in patients from RECORD-1 demonstrated that compared with placebo, everolimus 5 mg and 10 mg daily significantly slowed growth of mRCC target lesions, nontarget lesions, and new metastases ($P < 0.0001$), with the 10-mg daily dosing more effective than 5 mg daily in reducing growth of target lesions. Based on results from RECORD-1, in 2009, oral everolimus was approved in the United States for patients with mRCC who failed treatment with sunitinib or sorafenib and in Europe for patients who progressed on or after treatment with VEGF-targeted therapy.[78,79]

## Ridaforolimus

Preclinical investigations demonstrated that ridaforolimus inhibited proliferation of multiple tumor cell lines *in vitro* and *in vivo*, including tumors of breast, colon, lung, prostate, glial and pancreatic origin.[80,81] During a phase I evaluation of ridaforolimus in patients with advanced solid malignancies (including RCC), dosages of 3 to 28 mg IV once daily for 5 days were investigated and the MTD was 18.75 mg daily.[82] The antitumor activity of ridaforolimus was also observed in metastatic sarcoma and endometrial cancer cell lines and sensitivity was shown to correlate with the proportions of cells in G0/G1 phase of cell cycle proteins.[83] Assessment of dosing schedules, 10 mg daily and 10 mg daily for 5 days every other week or weekly found intermittent dosing not to be associated with the immunosuppressive effects observed with daily dosing.[84] Subsequently, intermittent dosing

was recommended for optimal antitumor activity and minimal systemic effects. Phase I studies with ridaforolimus IV in combination with paclitaxel or capecitabine demonstrated antitumor activity in patients with solid tumors including RCC.[85,86] Results from a phase II trial (NCT00093080) of ridaforolimus 12.5 mg IV once daily for 5 days every 2 weeks in patients with relapsed and/or refractory sarcomas reported a 29% clinical benefit response rate and a 2% partial response rate in patients with bone sarcoma, leiomyosarcoma and liposarcoma.[38–40]

An oral formulation is also being clinically evaluated in patients with soft-tissue and bone sarcomas. In the phase III SUCCEED (NCT00538239) trial, patients with metastatic sarcomas are receiving oral ridaforolimus 40 mg for 5 consecutive days each week or placebo. Interim results demonstrated a 3.2-week improvement in PFS in the maintenance setting following chemotherapy.[87,88]

## PK/PD profiles and mTOR pathway inhibition

Although temsirolimus and everolimus inhibit mTOR via a similar mechanism of action (MoA), the metabolism, formulations, dosing schedules and routes of administration are distinctively different, resulting in varying PK/PD profiles. Temsirolimus is an inactive soluble ester with low oral bioavailability, yet as an IV formulation, temsirolimus acts as prodrug which is metabolized to the active compound sirolimus.[34,89] The IV formulation of temsirolimus subsequently exploits the anticancer properties of sirolimus with improved pharmacokinetics without clinical evidence of immunosuppression.[89] In contrast, everolimus is orally bioavailable with no active metabolites.[59]

### Temsirolimus

In a phase I study of patients with advanced solid tumors who received temsirolimus 7.5- to 220-mg/m$^2$ weekly IV infusions, the maximum plasma drug concentration ($C_{max}$) and area under the plasma concentration curve (AUC) was shown to increase subproportionally with dose.[46] The mean volume of distribution at steady state ($VD_{ss}$) ranged from 127 to 384 liters and the sirolimus-to-temsirolimus ratio ranged from 2.5 to 3.5. Total body clearance (Cl) was shown to be nonlinear, ranging from 19 to 51 L/hour (34 to 220 mg/m$^2$). The PK parameters of temsirolimus were established in a randomized phase II study of patients with advanced RCC who received once-weekly IV doses of 25, 75 or 250 mg temsirolimus.[90] Data revealed dose, single versus multiple dose and body surface area were significant PK covariates.[90] AUC correlated with AE severity for thrombocytopenia, ($P = 0.007$), pruritus ($P = 0.011$) and hyperlipidemia ($P = 0.40$). Temsirolimus exposure also correlated with a subset of gene transcripts in PBMCs after 16 weeks of therapy ($P < 0.001$). Further results from a phase I PK study in patients with advanced cancer treated with IV temsirolimus 0.75 to 24 mg/m$^2$ once daily for 5 days every 2 weeks demonstrated that exposure increased less than proportionally with dose.[34] The elimination half-life ($t_{½}$) was 13 to 25 hours, and sirolimus was shown to be the main metabolite.

Phase I PK data of treatment with oral temsirolimus in patients with advanced cancer demonstrated extensive first-pass metabolism resulting in low bioavailability (1.5% to 2.5%).[53] However, when sirolimus concentration was also considered, relative exposure

($AUC_{oral}/AUC_{IV}$) ranged within the limits of oral sirolimus itself (from 8.8–26.5% compared with 18%, respectively). The MTD of the oral formulation was 75 mg for 5 days every 2 weeks, with 50% of patients requiring dose reductions.

In a PD evaluation of patients with mRCC ($n = 9$ from a subset of patients enrolled in a phase II study of temsirolimus[33]), a single dose of temsirolimus 25, 75 or 250 mg IV inhibited p70S6K activity in PBMCs, and inhibition was found to be independent of the administered dose.[91] There was also a significant linear association between time to disease progression and inhibition of kinase activity 24 hours after treatment ($P = 0.04$). However, due to the limited sample size, firm conclusions cannot yet be made regarding the value of p70S6K as a biomarker towards the prediction outcomes of patients treated with temsirolimus. Additionally, data from a large retrospective analysis have shown a rise in cholesterol levels to be associated with prolonged survival in temsirolimus-treated patients (OS: hazard ratio [HR] 0.76 per mmol/L, $P < 0.0001$; PFS: HR 0.81 per mmol/L, $P < 0.0001$). Although further prospective biomarker studies are warranted, these results suggest cholesterol increase may potentially serve as an important biomarker with respect to temsirolimus therapy and survival outcomes.[92]

### Everolimus

A phase I PK/PD study of oral everolimus in patients with advanced solid tumors demonstrated sustained inhibition of mTOR activity in tumor tissue at doses of ≥20 mg weekly or 5 to 10 mg daily.[59] The $t_{½}$ of oral everolimus was 30 hours (range 26 to 38 hours) and the AUC increased proportionally with dose while $C_{max}$ increased less than proportionally with doses ≥20 mg. Data from another phase I PK/PD tumor modelling study demonstrated time- and dose-dependent S6K1 inhibition in everolimus-treated PBMCs.[60] S6K1 inhibition in both rat and human PBMCs was associated with an antitumor effect and assessment of rat and human PK/PD models suggested daily administration of everolimus exerts greater antitumor activity than weekly administration.

Results from a phase I PD study conducted in patients with advanced solid tumors treated with everolimus weekly (20, 50 or 70 mg) or daily (5 or 10 mg) reported dose- and schedule-dependent inhibition of the mTOR pathway with near-complete inhibition at 10 mg daily or ≥50 mg weekly.[61] A comparison of these dosages in the tumor PD model demonstrated more profound and better maintained mTOR inhibition with the 10-mg daily dosage. Daily and weekly dose levels also resulted in maximal mTOR inhibition, as indicated by inhibition of peIF-4G and pS6 phosporylation. In the daily schedule, inhibition of peIF-4G was only complete at the 10-mg dose level, while in the weekly schedule, complete pS6 inhibition was observed at all dose levels. However, complete and prolonged inhibition of peIF-4G was observed only at doses ≥50 mg. Overall, 10 mg oral everolimus daily was considered the optimal dose, as it was shown to fully inhibit the phosphorylation of both markers.

## Clinical use of mTOR inhibitors in mRCC

National guidelines recommend temsirolimus for use in treatment-naive patients with poor prognosis (high MSKCC risk) mRCC of any histology (predominant clear-cell or non-clear

cell histology).[14–17] This recommendation is based on results from the global trial for Advanced Renal Cell Carcinoma (ARCC), a randomized, phase III study of temsirolimus versus IFN-α.[7] Patients enrolled in the trial were newly diagnosed (no previous systemic therapy was permitted) with primarily poor-prognosis mRCC (defined as individuals demonstrating at least 3 MSKCC predictors of short survival) of any histology type, including those with neurologically stable brain metastases. Patients were randomized to receive temsirolimus 25 mg IV weekly, IFN-α 3 times weekly or temsirolimus 15 mg IV weekly plus IFN-α 3 times weekly. For those who received temsirolimus only, median OS was 10.9 months compared with 7.3 months in those who received IFN-α. The combination of temsirolimus and IFN-α did not improve OS (8.4 months) over temsirolimus alone. Median PFS for patients treated with temsirolimus, IFN-α or both were 3.8, 1.9 and 3.7 months, respectively, as determined by site investigator's assessments. Based on these data, temsirolimus has a category 1 level recommendation for first-line treatment of poor-prognosis patients with relapsed or unresectable advanced RCC.[17]

Everolimus is standard-of-care therapy for patients with mRCC whose disease has progressed after previous VEGFr-TKI therapy.[14–17] This recommendation is based on evidence from Renal Cell Cancer treatment with Oral RAD001 given Daily (RECORD-1), a pivotal phase III trial of oral everolimus plus best supportive care (BSC) *vs* placebo plus BSC.[10] Patients with mRCC whose disease had progressed during treatment with prior sunitinib and/or sorafenib were randomized 2:1 to receive either everolimus 10 mg once daily or placebo. Patients were stratified by previous therapy (1 or 2 VEGFr-TKIs) and by MSKCC risk (favorable, intermediate or poor). Overall median PFS by independent central review was 4.9 months for patients who received everolimus and 1.9 months for patients who received placebo ($P < 0.001$). A pre-planned, prospective subanalysis of RECORD-1 also found everolimus to provide clinical benefit over placebo in patients who had received treatment with either 1 previous VEGFr-TKI ($n = 308$) or 2 previous VEGFr-TKIs ($n = 108$).[93] A trend toward longer PFS was observed in patients treated with 1 previous VEGFr-TKI (median PFS, 5.4 months) than in patients treated with 2 previous VEGFr-TKIs (median PFS, 4.0 months). Based on these results, everolimus has a category 1 level recommendation in patients with mRCC and predominant clear cell histology who have progressed on previous VEGFr-TKI therapy.[17]

Although no head-to-head studies comparing mTOR inhibitors in patients with mRCC have been conducted, a recent retrospective analysis evaluated effectiveness of second-line everolimus ($n = 233$), temsirolimus ($n = 178$) and sorafenib ($n = 123$) in VEGFr-TKI-refractory patients with mRCC.[94] Most patients received first-line sunitinib (86%) and most of them experienced disease progression (86%). After adjusting for baseline characteristics, OS was significantly prolonged for everolimus compared with temsirolimus (HR 0.56; 95% CI 0.40–0.78; $P < 0.001$) and sorafenib (HR 0.65; 95% CI 0.42–0.99; $P = 0.047$). Median PFS was significantly longer for everolimus than for temsirolimus (HR 0.73; 95% CI 0.55–0.96; $P = 0.025$) and, although not statistically significant, longer than for sorafenib (HR 0.75; 95% CI 0.53–1.07; $P = 0.110$). Results of this analysis suggest that VEGFr-TKI-refractory patients with mRCC who receive second-line everolimus experience a greater survival benefit than patients who receive second-line temsirolimus or sorafenib.

## Future directions

In the majority of patients with mRCC, targeted therapies do not produce complete responses and most individuals eventually become refractory to treatment. Additional novel agents are therefore warranted to provide further clinical benefit in this setting (Table 3).[95–102] ***mTORC1/mTORC2 kinase domain inhibitors***[95,103–105]: mTORC1 controls cell growth in response to nutrients and growth factors, and regulation is associated with oncogenic PI3K activity; mTORC2 mediates activity involved in cancer cell transformation and survival. By binding to the ATP binding site of the kinase domain of mTOR, these agents simultaneously inhibit both mTOR complexes, TORC1 (rapamycin sensitive) and TORC2 (rapamycin insensitive). ***mTOR/PI3K dual inhibitors***: high PI3K and mTOR expression observed in patients with RCC is associated with decreased survival, providing the rationale to synergistically target coexpression of these two proteins.[102] ***PI3K-selective inhibitors***: another class of agents focusing on the PI3K pathway, a pathway which is constitutively activated in RCC cells regardless of VHL status and is associated with adverse clinical outcomes.[102] ***Programmed cell death 6 (PDCD6) modulators***: the pro-apoptotic protein PDCD6 has been shown to suppress phosphorylation of signalling regulators downstream from PI3K, including Akt, mTOR, and p70S6K. Binding of PDCD6 to VEGFr-2 plays a key role in the PI3K/mTOR/p70S6K signalling pathway and subsequently in modulating cellular angiogenesis.[106]

## Summary and Conclusions

mTOR inhibitors have similar mechanisms of action; however, because of differences in their metabolism (prodrug versus orally bioavailable), their formulations (IV versus oral) and their schedules of administration (weekly versus daily), they possess distinct PK/PD profiles, leading to their application for a variety of RCC treatment niches. To date, the effect of temsirolimus on mTOR pathway activity has been evaluated in only a limited number of patients, and the degree of mTOR pathway inhibition does not appear to correlate with administered dose. However, available evidence has shown 25-mg IV weekly dosing of temsirolimus has a significant antitumor effect in patients with poor-risk mRCC based on the results of the ARCC study.[7] On the other hand, an oral dose of everolimus 10 mg daily provides sustained inhibition of mTOR signalling, and results from RECORD-1 have shown this dosage to correlate with significant antitumor effect in patients with mRCC.[10,13]

mTOR inhibitors as a class provide clinical benefit to patients with mRCC and other cancer types. Clinical trials of mTOR inhibitors in a variety of tumor types are ongoing, including evaluation of ridaforolimus, as a maintenance therapy in patients with metastatic sarcoma (NCT00538239). In the RCC setting, temsirolimus is recommended as first-line treatment for patients with mRCC who are of poor MSKCC risk.[14–17] In contrast everolimus is recommended in patients with mRCC who have failed previous treatment with VEGFr-TKIs.[14–17] While these agents form an intricate part of the mRCC targeted therapy toolbox, the majority of patients ultimately become refractory to treatment with mTOR inhibitors. For such individuals, simultaneous targeting of multiple members of the PI3K/Akt/mTOR pathway may provide additional clinical benefit. With respect to targeted therapies among

the various cancer settings, the role of mTOR inhibitors continues to evolve across the mRCC treatment landscape.

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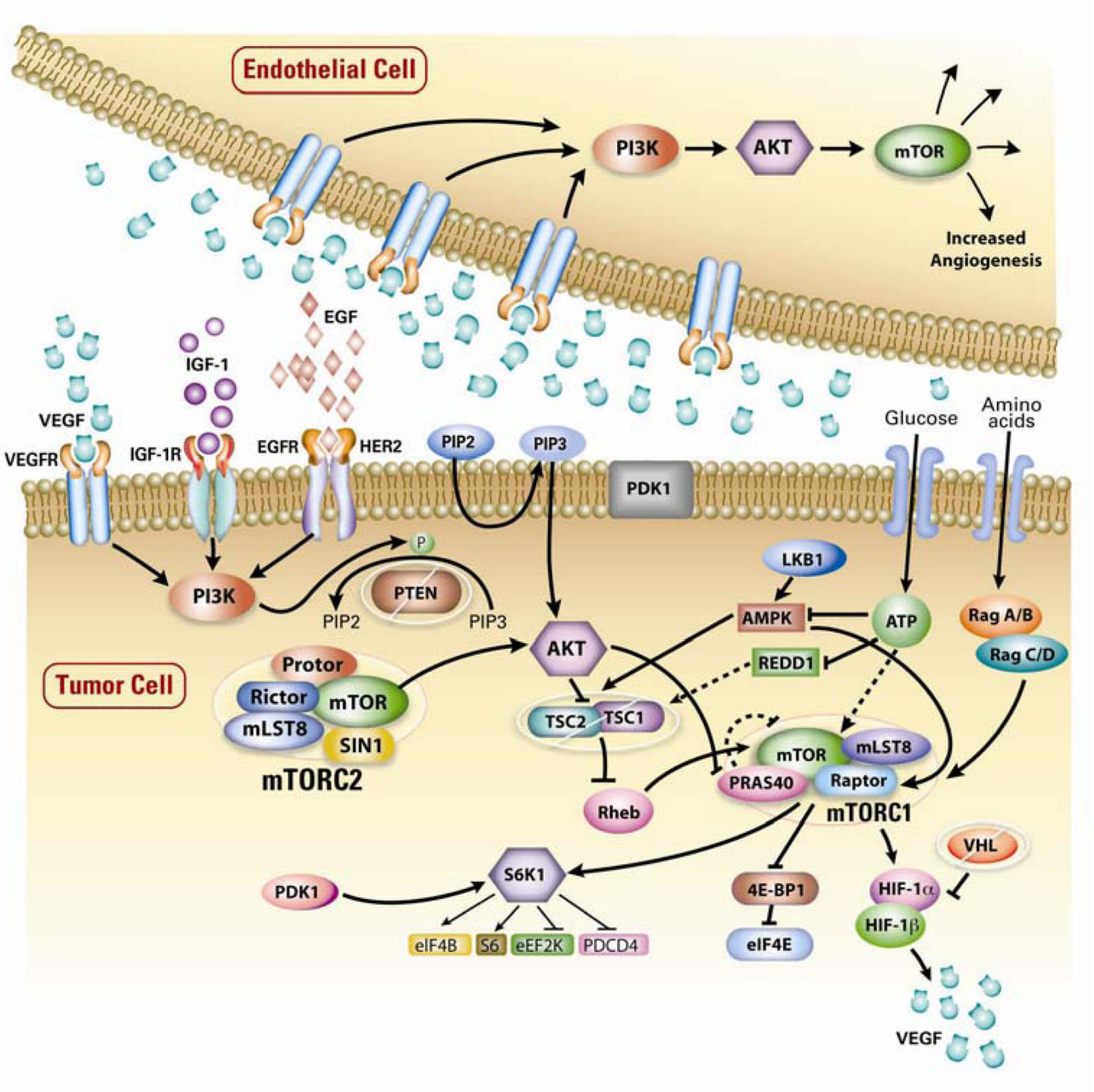


**Figure 1. mTOR signalling pathway in cancer**[20]

mTOR is a serine/threonine kinase that regulates protein synthesis necessary for cell growth, proliferation, metabolism and angiogenesis. The binding of growth factors to cell surface receptors, such as VEGFr, IGF-receptor (IGF-1r) and EGFr, and by nutrients (amino acids and glucose) entering the cell, subsequently stimulate the mTOR signaling pathway. Key upstream elements include PI3K and AKT involved in the phosphorylation and activation of mTOR. Intracellular kinase PI3K synthesizes membrane phospholipids responsible for activation of the kinase AKT while negative regulator PTEN reverses PI3K activity and suppresses AKT activation. Activation of AKT facilitates phosphorylation of the tuberous

sclerosis tumor suppressor gene TSC2 and leads to inactivation the TSC1-2 complex, a key regulator of mTORC1. mTORC1 controls essential signal transduction pathways via its downstream effectors S6K1 and 4E-BP1 and coordinates the production of the transcription factor HIF-1α. Promotion of transcription of angiogenic factors such as VEGF is regulated by HIF-1α in complex with HIF-1β. Dysregulation of the PI3K/AKT/mTOR pathway is observed in many cancers. A number of mechanisms are responsible for hyperactive mTOR signaling including overexpression or activation of growth factor receptors, activation of mutations in PI3K/AKT and decreased expression of PTEN, TSC1–2 or VHL. In this figure, activation is depicted as an arrow while inhibition is represented as a bar.
4E-BP1, 4E-binding protein 1; HIF-1α, hypoxia-inducible factor-1α; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; PTEN, phosphatase and tensin homolog; S6K1, S6 kinase 1; TSC, tuberous sclerosis complex; VHL, von Hippel-Lindau.

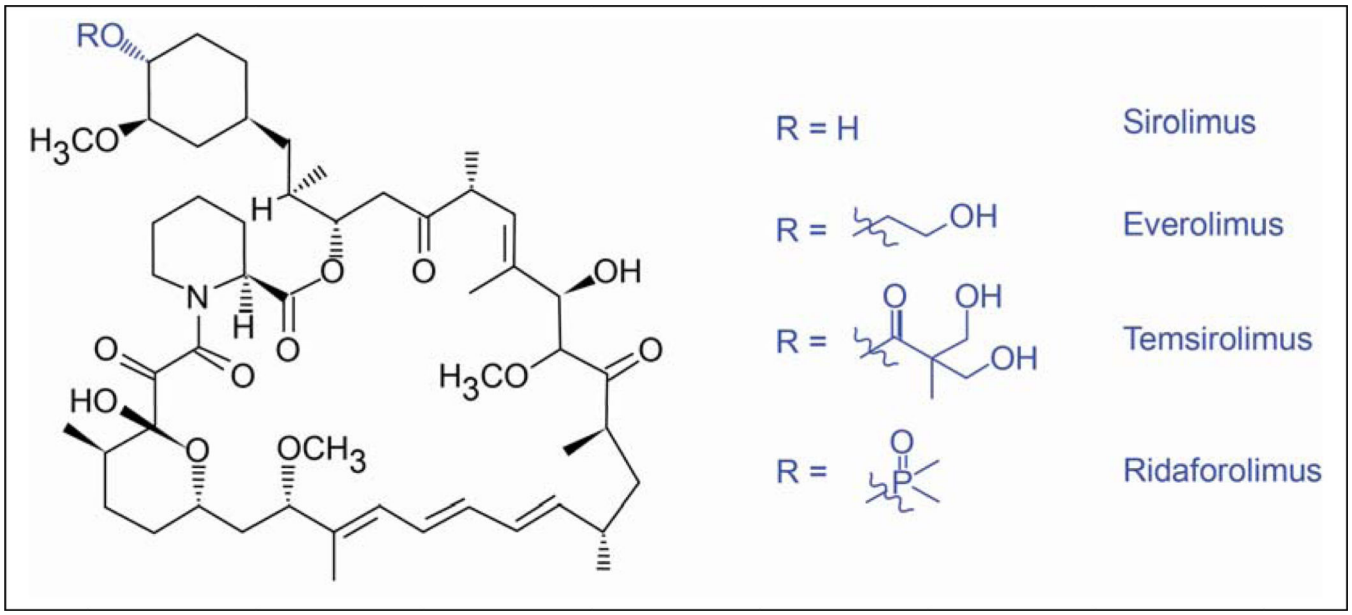


**Figure 2. Rapamycin and its analogs**

Structural derivatives of the macrocyclic lactone sirolimus (also termed rapamycin) include: temsirolimus (42-[2,2-bis (hydroxymethyl)] rapamycin, also known as CCI-779); everolimus (42-O-(2-hydroxyethyl) rapamycin, also known as RAD001); ridaforolimus (macrolide dimethylphophinic acid rapamycin-40-O-yl ester derivative of sirolimus, also known as deforolimus).

**Table 1**

Completed Oncology Trials of Temsirolimus (IV administration)

| Study | Patient Population (*N*) | Treatment | Efficacy | Safety |
|---|---|---|---|---|
| Phase I dose escalation[46] | Advanced cancer (24) | Temsirolimus 7.5–220 mg/m$^2$ weekly | PR: *n* = 2 | Treatment-related acne-like, maculopapular rashes and mucositis or stomatitis |
| Phase I[34] | Advanced cancer (63) | Temsirolimus 0.75–24 mg/m$^2$ | PR, *n* = 4 (3 unconfirmed)<br>SD, *n* = 2 | Treatment-related asthenia, mucositis, nausea and cutaneous toxicity |
| Phase II[33] | Metastatic renal cell carcinoma (111) | Temsirolimus 25, 75 or 250 mg weekly | ORR: 7%<br>CR: *n* = 1<br>PR: *n* = 7<br>Minor response: 26%<br>TTP: 5.8 months<br>OS: 15.0 months | Grade 3/4 hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), hypertriglyceridemia (6%) |
| Phase I/II[48] | Metastatic renal cell carcinoma (39) | Temsirolimus 15 mg weekly plus interferon-α | PR: *n* = 3<br>SD: *n* = 14<br>PFS: 7.6 months | Grade 3/4 leukopenia, hypophosphatemia, asthenia, anemia, hypertriglyceridemia |
| Phase III[7] | Metastatic renal cell carcinoma (626) | Temsirolimus 25 mg weekly<br>Interferon-α<br>Temsirolimus 15 mg weekly + interferon-α | ORR: 8.6%, 4.8%, 8.1%<br>OS: 10.9, 7.3, 8.4 months<br>PFS:<br>3.8, 1.9, 3.7 months (local)<br>5.5, 3.1, 4.7 months (independent) | Temsirolimus: grade 3/4 anemia (20%), asthenia (11%), hyperglycemia (11%), dyspnea (9%), infection (5%) |
| Phase II[35] | Locally advanced or metastatic breast cancer (109) | Temsirolimus 75 or 250 mg weekly | ORR: 9%<br>PR: *n* = 10<br>TTP: 12.0 weeks | Grade 3/4 mucositis (9%), leukopenia (7%), hyperglycemia (7%), somnolence (6%), thrombocytopenia (5%) and depression (5%) |
| Phase III[51] | Postmenopausal locally advanced BC or mBC | Temsirolimus 30 mg daily for 5 days every 2 weeks + letrozole 2.5 mg daily (*n* = 556)<br>Placebo + letrozole 2.5 mg daily (*n* = 556) | Temsirolimus + letrozole,<br>PFS: 8.8 months<br>ORR: 27%<br>CR: *n* = 11<br>PR: *n* = 139<br>SD: *n* = 100<br>Placebo + letrozole,<br>PFS: 8.9 months<br>ORR: 27%<br>CR: *n* = 11<br>PR: *n* = 139<br>SD: *n* = 106 | Temsirolimus + letrozole, grade 3/4 hyperglycemia (4%), dyspnea (3%), neutropenia (3%), asthenia (3%)<br>Placebo + letrozole, grade 3/4 dyspnea (3%), asthenia (2%), hyperglycemia (1%), neutropenia (1%) |
| Phase II[47] | Mantle cell lymphoma (35) | Temsirolimus 250 mg weekly | ORR: 38%<br>CR: *n* = 1<br>PR: *n* = 12<br>TTP: 6.5 months<br>DOR: 6.9 months | Grade 3/4 thrombocytopenia (66%), neutropenia (29%), anemia (26%) |
| Phase II[50] | Mantle cell lymphoma (29) | Temsirolimus 25 mg weekly | ORR: 41%<br>CR: *n* = 1<br>PR: *n* = 10<br>TTP: 6 months<br>DOR: 6 months | Grade 3/4 thrombocytopenia (39%), fatigue (25%), neutropenia (18%), anemia (15%) |
| Phase III[36] | Mantle cell lymphoma (162) | Temsirolimus 175 mg weekly for 3 weeks then: 75 mg, 25 mg or investigators choice | ORR, 22%, 6%, 2%<br>PFS: 4.8, 3.4, 1.9 months<br>OS: 12.8, 10.0, 9.7 months<br>CR: *n* = 1, 0, 1<br>PR: *n* = 11, 3, 0 | Grade 3/4 thrombocytopenia (59%, 52%, 36%), anemia (20%, 11%, 17%), neutropenia (15%, 22%, 26%), asthenia (13%, 19%, 8%) |
| Phase II[49] | Recurrent or metastatic endometrial carcinoma, chemotherapy-naive (33, | Temsirolimus 25 mg weekly | Chemotherapy-naïve<br>PR: *n* = 7<br>SD: *n* = 20 | Chemotherapy-naive: grade 3 fatigue (12%), diarrhea (6%), pneumonitis (6%) |

| Study | Patient Population (*N*) | Treatment | Efficacy | Safety |
|---|---|---|---|---|
| | 29 evaluable for tumor response) or chemotherapy-treated (27, 25 evaluable for tumor response) | | Chemotherapy-treated: PR: *n* = 2 SD: *n* = 12 | Chemotherapy-treated: grade 3 fatigue (11%), diarrhea (11%), pneumonitis (11%), dyspnea (7%), grade 3/4 hypokalemia (11%) |

ORR, overall response rate; OS, overall survival; TTP, time-to-progression; DOR, duration of response; PR, partial response; CR, complete response.

**Table 2**

Completed Oncology Trials of Everolimus (Oral Administration).

| Study | Patient Population (*N*) | Treatment | Efficacy | Safety |
|---|---|---|---|---|
| Phase I[62] | Advanced NET (22, 21 evaluable for response/ toxicity) | Everolimus 5–10 mg plus pasireotide sc 600–900 μg plus pasireotide 40–60 mg | PR: *n* = 1<br>SD: *n* = 19 | Treatment related hyperglycemia, hypophosphatemia, thrombocytopenia, lymphopenia, elevated alkaline phosphatase, mucositis, prolonged QTc and joint pain |
| Phase II[63] | Metastatic pNET (160) | Everolimus 10 mg (*n* = 115) or Everolimus 10 mg plus octreotide LAR (*n* = 45) | Everolimus,<br>PR: *n* = 11<br>SD: *n* = 78<br>PFS: 9.7 months<br>Everolimus plus octreotide LAR,<br>PR: *n* = 2<br>SD: *n* = 36<br>PFS: 16.7 months | Grade 3/4 asthenia and thrombocytopenia |
| Phase III[37] | Advanced pNET (410) | Everolimus 10 mg daily continuous plus BSC (*n* = 207)<br>Placebo plus BSC (*n* = 203) | PFS:<br>Everolimus,<br>11.0 months (73% cross over)<br>Placebo,<br>4.6 months | Grade 3/4 stomatitis (7%, 0%), anemia (6%, 0%), hyperglycemia (5%, 2%) |
| Phase III (RADIANT-2 substudy)I[64] | Advanced NET (429) | Everolimus plus octreotide LAR (*n* = 216)<br>Placebo plus octreotide LAR (*n* = 213) | PFS: Everolimus plus octreotide LAR, 14.3 months (prior SSA), 25.2 months (no prior SSA)<br>Placebo plus octreotide LAR, 11.1 months (prior SSA), 13.6 months (no prior SSA) | NR |
| Phase II[65] | Metastatic renal cell carcinoma (39) | Everolimus 10 mg daily continuous | PFS: 11.2 months<br>OS: 22.1 months<br>PR: *n* = 5<br>SD: *n* = 21 | Grade 3/4 pneumonitis (18%); transaminase elevations (10%); thrombocytopenia, hyperglycemia and alkaline phosphatase elevations (8% each); and hyperlipidemia (5%) |
| Phase III[10] | Metastatic renal cell carcinoma (416) | Everolimus 10 mg daily continuous (*n* = 277)<br>Placebo (*n* = 139) | PFS:<br>Everolimus, 4.9 months<br>Placebo, 1.9 months<br>OS (80% cross over):<br>Everolimus, 14.8 months<br>Placebo, 14.4 months | Grade 3/4 decreased lymphocytes (16%, 2%), increased glucose (15%, <1%), decreased hemoglobin (12%, 1%), infections (7%, 3%), dyspnea (6%, 1%), fatigue (5%, 0%), stomatitis (4%, <1%) |
| Phase Ib[66] | HER-2 negative mBC (16, 13 evaluable for response) | Everolimus 20–30 mg weekly + cisplatin 25 mg/m$^2$ with paclitaxel 80 mg/m$^2$ once weekly for 3 weeks (4 week cycle) | TTP: 5.0 months<br>CR: *n* = 1<br>PR: *n* = 2<br>SD: *n* = 7 | Grade 3/4 neutropenia (8.5%) |
| Phase II[67] | Recurrent mBC(49) | Everolimus 10 mg daily (*n* = 33)<br>Everolimus 70 mg weekly (*n* = 16) | CR: *n* = 1<br>PR: *n* = 3<br>SD: *n* = 5 | Grade 3/4 fatigue, pneumonitis, infection and neutropenia |
| Phase Ib[68] | Pretreated with trastuzumab mBC (33) | Everolimus 5–10 mg daily + paclitaxel/ trastuzumab (*n* = 23)<br>Everolimus 30 mg weekly + paclitaxel/ trastuzumab (*n* = 10) | Daily everolimus + paclitaxel/trastuzumab, PFS: 33 weeks<br>CR: *n* = 2<br>PR: *n* = 7<br>SD: *n* = 8 | Grade 3/4 neutropenia (57%, 40%), leukopenia (35%, 20%), lymphopenia (30%, 40%), stomatitis (17%, 30%) |

| Study | Patient Population (*N*) | Treatment | Efficacy | Safety |
|---|---|---|---|---|
| | | | Weekly everolimus + paclitaxel/trastuzumab, PFS: 40.7 weeks<br>CR: *n* = 0<br>PR: *n* = 3<br>SD: *n* = 5 | |
| Phase II[69] | Trastuzumab and taxane-refractory HER2-positive mBC (55) | Everolimus 10 mg daily + paclitaxel/trastuzumab | PFS: 26 weeks<br>CR: *n* = 0<br>PR: *n* = 9<br>SD: *n* = 30 | Grade 3/4 neutropenia (28%), stomatitis (20%), lymphopenia (14%) |
| Phase Ib[70] | HER2-positive mBC (50) | Everolimus 5 mg daily + trastuzumab ± vinorelbine (*n* = 30)<br>Everolimus 20–30 mg daily + trastuzumab ± vinorelbine (*n* = 20) | PFS:<br>Daily everolimus + trastuzumab ± vinorelbine, 30.7 weeks<br>Weekly everolimus + trastuzumab ± vinorelbine, 27.1 weeks | Daily everolimus + trastuzumab ± vinorelbine: Grade 3/4 neutropenia (83%), leukopenia (47%), stomatitis (17%)<br>Weekly everolimus + trastuzumab ± vinorelbine: Grade 3/4 neutropenia (90%), leukopenia (40%), lymphopenia (15%) |
| Phase I/II[71] | Trastuzumab-resistant HER2-positive advanced breast cancer (47) | Everolimus 10 mg daily + trastuzumab (8 mg/kg, then 6 mg/kg every 3 weeks) | PR: *n* = 7<br>SD: *n* = 9 | Grade 3/4 hyperglycemia (13%), lymphopenia (13%), neutropenia (9%), diarrhea (9%), fatigue (9%), mucositis (9%), hypokalemia (6%) |
| Phase II[72] | Postmenopausal ER-positive operable breast cancer (270) | Everolimus 10 mg daily + neoadjuvant letrozole 2.5 mg daily (*n* = 138)<br>Placebo + neoadjuvant letrozole 2.5 mg daily (*n* = 132) | Everolimus + letrozole, ORR: 68%<br>CR: *n* = 18<br>PR: *n* = 76<br>Placebo + letrozole, ORR: 59%<br>CR: *n* = 12<br>PR: *n* = 66 | Everolimus + letrozole: Grade 3/4 hyperglycemia (5%), stomatitis (2%), pneumonitis (2%)<br>Placebo + letrozole: Grade 3/4 asthenia (<1%), arthralgia (<1%), cellulitis (<1%) |
| Phase II[73] | ER-positive AI refractory (11) | Everolimus 10 mg daily + fulvestrant 500 mg day 1, 250 mg day 14, 250 mg day 28, and monthly thereafter | CBR: 55%<br>TTP: 8.6 months | Mucositis (63.6%), rash (45.5%), infection (36.4%), fatigue (27.3%) |
| Phase II[74] | Postmenopausal ER-positive advanced breast cancer (111) | Everolimus 10 mg daily + tamoxifen 20 mg daily (*n* = 54)<br>Tamoxifen 20 mg daily (*n* = 57) | Everolimus + tamoxifen, CBR at 6 months: 61%<br>TTP: 8.6 months<br>OS: NR<br>Tamoxifen alone, CBR at 6 months: 42%<br>TTP: 4.5 months<br>OS: 32.9 months | Grade 3/4 stomatitis (11%, 0%), pain (9%, 18%), anorexia (7%, 4%), infection (7%, 5%), fatigue (6%, 11%), nausea (4%, 0%), rash (4%, 0%), diarrhea (2%, 0%), pneumonitis (2%, 4%) |
| Phase III[56,75] | Postmenopausal ER-positive advanced breast cancer (724) | Everolimus 10 mg daily + exemestane 25 mg daily (*n* = 485)<br>Placebo + exemestane 25 mg daily (*n* = 239) | Everolimus + exemestane, PFS: 7.4 months<br>CR: *n* = 3<br>PR: *n* = 83<br>SD: *n* = 521<br>Placebo + exemestane, PFS: 3.2 months<br>CR: *n* = 0<br>PR: *n* = 9<br>SD: *n* = 430 | Everolimus + exemestane: Grade 3/4 stomatitis (8%, 0%), anemia (5%, 1%), hyperglycemia (4%, <1%), dyspnea (4%, 0%), fatigue (3%, <1%)<br>Placebo + exemestane: Grade 3 3/4 increased alanine aminotransferase (2%, 0%), dyspnea (1%, <1%), stomatitis (1%, 0%), fatigue (1%, 0%), diarrhea (1%, 0%), back pain (1%, 0%) |
| Phase II[76] | Recurrent endometrial carcinoma (35, 28 evaluable for efficacy) | Everolimus 10 mg daily for 28 day cycles | SD at 8 weeks: *n* = 12<br>CBR at 20 weeks: *n* = 6 | Treatment-related fatigue, anemia, pain, lymphopenia and nausea |

AI, aromatase inhibitor; CR, complete response; CBR, clinical benefit rate; DOR, duration of response; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NET, neuroendocrine tumor; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; SSA, long-acting somatostatin analog; TTP, time-to-progression.

**Table 3**

Targeted Agents in Development

| Study | Agent | Activity |
|---|---|---|
| Preclinical[95] | PP242 and PP30 (TORC2 inhibitors) | Inhibits TORC2; blocks phosphorylation of Akt and S473; inhibits proliferation of primary cells more completely than rapamycin |
| Preclinical, *in vitro* and *in vivo* cancer models[96] | WYE-125132 (TORC1 and TORC2 inhibitors) | Inhibits TORC1 and TORC2; inhibits cancer cell growth and survival, protein synthesis, cell size, bioenergetic metabolism and adaptation to hypoxia |
| Preclinical *in vitro* and *in vivo*[97] | WAY-600, WYE-687, WYE-354 (pyrazolopyrimidine ATP-competitive mTOR inhibitors) | Block substrate phosphorylation by TORC1 and TORC2 in response to growth factor amino acids and hyperactive PI3K/Akt |
| Preclinical (RCC cell lines and xenografts)[98] | NVP-BEZ235: dual PI3K/mTOR inhibitor | Inhibition of Akt and S6 phosphorylation, induction of apoptosis, and reduction in markers of tumor cell proliferation |
| Preclinical (renal cell carcinoma lines and RCC xenografts in nude mice)[99] | NVP-BEZ235: dual PI3K/mTOR inhibitor; little antiangiogenic activity | Antitumor activity alone and increased when combined with sorafenib |
| Phase I, patients with advanced solid tumors[100] | BEZ235: PI3K inhibitor | BEZ235 exhibited dose- and day-dependent PI3K inhibition as measured by elevation of plasma C-peptide levels; 14 of 51 evaluable patients had SD ≥4 months; tumors from 6 of these 14 patients carried dysregulations of the PI3K pathway; 18 of 35 evaluable patients had detectable decreases of $^{18}$FDG uptake |
| Preclinical (cancer cell line)[101] | PF-04691502: ATP-competitive dual inhibitor of PI3K/mTOR | Reduced phosphorylation of Akt and inhibited cell proliferation; inhibited TORC1 activity and activation of PI3K and mTOR downstream effectors (including S6RP and Akt) |
| Preclinical (RCC cell lines)[102] | LY294002: PI3K inhibitor | LY294002 plus rapamycin synergistically inhibited cell growth |

SD, stable disease.