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mTOR Inhibitors in Advanced Renal Cell Carcinoma

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Better understanding of the genetics and molecular biology of renal cell carcinoma (RCC) has led to the development of several targeted agents, 6 of which have previously received FDA approval for treatment advanced disease based on large international phase III trials.[1–6]

Four of these compounds (sunitinib, sorafenib, pazopanib, and bevacizumab) inhibit tumor angiogenesis through blockade of vascular endothelial growth factor (VEGF). A second class of agents includes the intravenously administered temsirolimus and the oral compound everolimus, which both exhibit anti-tumor effects through inhibition of the mammalian target of rapamycin (mTOR). The mechanisms of action, clinical data leading to approval, clinical use of mTOR inhibitors, as well as current understanding of the molecular mechanisms behind resistance to this class of drugs are reviewed here.

BIOLOGY AND MECHANISM OF ACTION

The phosphatidyl-inositol-3 kinase (PI3K) / Akt / mTOR pathway is a molecular signaling axis with key impact on various integral cellular functions including protein synthesis, glucose metabolism, cellular migration, and cell survival. It has been implicated in promoting tumor growth.[7,8] The pathway is affected by growth factors (EGF, IGF1, FGF), hormones (estrogen, thyroid hormones), vitamins, integrins, intracellular calcium, and the *ras*-dependent MAPK pathway. Binding of insulin or insulin-like growth factors to their respective receptors leads to recruitment of PI3K. Once activated, PI3K converts phosphatidylinositol-4,5-phosphate (PIP2) to phosphatidylinositol-3,4,5-phosphate (PIP3), which in turn activates Akt/PKB, a serine/threonine kinase. PI3K signaling is inhibited by action of the tumor suppressor phosphatase and tensin homolog (PTEN), which negatively affects formation of PIP3, thus limiting Akt activity.[9] Activated Akt promotes several biological processes through phosphorylation of various downstream targets, and indirectly activates mTOR, a highmolecular-weight serine threonine kinase. Specifically, activated Akt phosphorylates tuberous sclerosis complex 2 (TSC2), leading to disassociation of the TSC1/

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TSC2 heterodimer complex, and inhibiting the ability of TSC2 to act as a GTPase activating protein. This allows Rheb (Ras homologue enriched in the brain), an activator of mTOR, to remain GTP bound and thus active.[10] In addition to and independent of upstream signaling through PI3K, mTOR integrates other stimuli including nutrients (also through TSC1/2 and Rheb), cellular energy levels, and cellular stress.[11] In normal cells, this helps to coordinate cell-cycle progression from G1 to S phase; in tumorigenesis, however, deregulation of components in this intricate system promotes growth and proliferation of malignant clones.

Once activated, mTOR exerts its action via protein synthesis and affects various cellular functions including cell growth, proliferation, angiogenesis, and metabolism.[11] The latter includes effects on glucose and lipid control, [12,13] which has implications for therapeutically targeting mTOR. mTOR been found to act through 2 structurally and functionally distinct multiprotein signaling complexes, mTOR complex 1 (mTORC1, comprising mTOR and a scaffolding protein termed regulatory-associated protein of mTOR [raptor]) and mTOR complex 2 (mTORC2, comprising mTOR and a scaffolding protein termed rapamycin insensitive companion of mTOR [rictor]). [8,11]

Activation of mTORC1 takes place indirectly through inhibition of its repressor TSC2 as outlined above. The main downstream targets of mTORC1 are the ribosomal S6 kinase (p70S6K) and the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1). Phosphorylation of 4E-BP1 through mTORC1 results in the release of 4E-BP1 from the eukaryotic translation initiation factor (eIF4E), which is then freed to interact with eIF4 G and other proteins to assemble the mammalian ribosome initiation complex eIF4F.[14] In cancer cells, 4E-BP1 phosphorylation eventually results in the initiation of translation. The activation of mTORC1 downstream targets, through its effect on protein synthesis, modulates activity of cellcycle-regulating proteins, HIF1α, FGF, VEGF, STAT3, cyclin-D, and c-Myc.[15–17]

In the pathogenesis of RCC, regulation of HIF, a known oncologic driver of the disease, appears specifically relevant and possibly central to the antitumor effects of mTOR inhibitors.[18]

The details of mTORC2 functions are less well understood. Once active, mTORC2 phosphorylates the hydrophobic motif of the AGC kinase family, including Akt (S^{473}), thereby inducing Akt activation.[19] Other possible downstream targets with effect on cell survival, proliferation, and cytoskeleton include the Forkhead box, class O (FOXO) class of transcription factors,[20] protein kinase C alpha (PKCα), and the serum/glucocorticoid regulated kinase 1 (SGK1).[21] Translation of HIF2α depends upon the activity of mTORC2 but not mTORC1, whereas HIF1α expression depends upon both mTORC1 and mTORC2. [22] These findings are significant, as most conventional RCC possesses biallelic alterations in the *VHL* gene, resulting in the accumulation of both HIF1α and 2α. Despite overlapping effects on gene expression, HIF2α is more relevant to the development and progression of RCC since it preferentially activates VEGF, RGFα, Oct4, and Cyclin D1.[23] In preclinical models, HIF2α suppression prevented tumor formation in pVHL defective renal carcinoma cells.[24] Importantly, mTORC2 activity is unaffected by rapamycin and its analogues, the mTOR inhibitors currently used in common practice. Consequently, HIF1α levels decrease, but HIF2α remains unaffected by rapamycin in preclinical RCC models.[25]

PI3K/AKT/MTOR IN RCC

One study examined 128 primary RCCs, 22 metastatic RCCs, and 24 nonneoplastic (normal) kidneys, and found the expression levels of p70S6K, p-mTOR, and pAkt significantly higher in RCC than in normal kidneys, both by immunohistochemistry and protein levels.[26] Similarly, another group found increased levels of phospho-S6 and/or

phospho-mTOR in the majority of 29 clear cell RCC tumors by immunohistochemistry.[27] A more recent report looking at 132 metastatic RCC samples, a subset with matched primary tumors, and an additional 10 sections from healthy kidney tissues found strong expression of various mTOR pathway proteins[28]. The authors reported significantly higher immunoreactivity scores for PI3K, p-mTOR, p-AKT and p70S6 in metastatic lesions compared to non-neoplastic proximal tubular epithelial cells. Notably, there were almost no cases of *PTEN* gene deletion in this series. There was no significant correlation between primary tumors and metastatic samples in matched pairs, suggesting that hyper activation of the pathway may contribute to the metastatic progress. Patients with shorter disease-free intervals showed significantly higher expression of PI3K (P=.035)[28]. Similarly, a separate report in primary RCC correlated mTOR pathway activation with survival and poor pathologic prognostic features.[29]

RAPAMYCIN AND ITS ANALOGUES

Rapamycin (also termed sirolimus) was originally identified as a natural antifungal antibiotic isolated from the bacteria Streptomyces hygroscopicus in the 1970s [30,31] and eventually led to the discovery of mTOR, the 'mammalian target of rapamycin'. Due to its ability to potently inhibit T-cell function, rapamycin was initially mainly used as an immunosuppressant in recipients of solid organ transplantation [32], but subsequently was found to be an attractive candidate for application in oncology due to its antitumor activity including preclinical models for RCC [33–35]. Several analogues of rapamycin have been developed to improve solubility and bioavailability. These include temsirolimus, and everolimus, and are termed 'rapalogues'. They share the same mechanism of action, and have been successfully applied in the treatment of various solid and hematologic malignancies [36,37]. Rapamycin and its analogues do not directly inhibit the mTOR kinase. Instead, they bind with high affinity to the FK-binding protein 12 (FKBP-12), an abundant intracellular immunophilin. The resulting complex potently inhibits the kinase activity of mTORC1, but has no suppressive effects on mTORC2 [17,38].

TEMSIROLIMUS[1]

Temsirolimus (Torisel®; Pfizer, New York, NY, USA) is a water-soluble prodrug of rapamycin with an added ester at the C43 position. It is rapidly metabolized to sirolimus through deesterification; both are potent binders of FKBP-12, and each forms an inhibitory complex with subsequent suppression of mTORC1 activity.

Phase I and II Studies

Preclinical studies demonstrating temsirolimus activity in a variety of human cancers[39–42] were fortified by promising results in phase 1 studies.[43–45] Intermittent schedules abrogated immunosuppressive effects without significant loss in antitumor activity. Responses included patients with advanced RCC. This led to a dedicated phase II trial in advanced refractory RCC.[46] With a primary endpoint of objective tumor response rate, 111 patients were randomized to 25, 75, or 250 mg of temsirolimus weekly by intravenous infusion. Patients were heavily pretreated (51% had received ≥ 2 prior immunotherapies) with extensive disease (83% had ≥ 2 sites of metastases). The objective response (OR) rate was 7% (1 complete response [CR], 7 partial responses [PR]); 51% had stable disease (SD) for ≥ 24 weeks or an OR. Median time to progression (TTP) was 5.8 months for the entire group, 6.3, 6.7, and 5.2 for patients in the 25-, 75-, and 250-mg groups, respectively. Median overall survival (OS) was 15 months; 13.8, 11.0, and 17.5 for patients in the 25-,75-, and 250-mg groups, respectively. Maculopapular rash (76%) and mucositis (70%) were the most frequent treatment-related toxicities; the most common grade 3/4 adverse events (AEs) included hyperglycemia (17%), hypophosphatemia (13%), anemia 9(%) and

hypertriglyceridemia (6%). Importantly, overall response rates (ORR) and OS were comparable for all dose levels. Dose reductions and treatment discontinuations were more frequent at higher doses. A subgroup analysis by Memorial Sloan-Kettering Cancer Center (MSKCC) risk group, developed for patients treated with interferon-α (IFN-α),[47] demonstrated > 2-fold survival differences between good/intermediate versus poor-risk patients at each dose level. Compared with historical data for IFN-α, treatment benefit was most striking for the poor-risk population.

Phase III Data

The Global Advanced Renal Cell Carcinoma (Global ARCC) phase III trial, conducted between 2003 and 2005, compared temsirolimus to IFN-α, or the combination, in advanced RCC.[4] Entry criteria allowed all histologic subtypes, but required participants to have at least 3 of 6 predictors of short survival (Table 1). Patients were randomized to 1 of 3 arms: temsirolimus 25 mg IV once weekly, IFN-α 3 million U subcutaneously 3 × week (escalated to 18 million U 3 × week, if tolerated), or a combination of temsirolimus 15 mg IV weekly and IFN 3 million U (escalated to 6 million U 3 × week). Efficacy at the second planned interim analysis of the intent-to-treat population revealed superior survival for temsirolimus over IFN-α but no improved survival for the combination over IFN-α alone. Median OS was 7.3, 10.9, and 8.4 months for IFN-α, temsirolimus, and the combination group, respectively. Progression-free survival (PFS) was significantly longer in patients receiving temsirolimus, with median PFS times of 1.9, 3.8, and 3.7 months for the IFN-α, temsirolimus, and the combination group, respectively (P<.001). The proportion of patients with SD ≥6 months or an OR was significantly greater for patients receiving temsirolimus alone (32.1%) or in combination (28.1%) than in the IFN-α group (15.5%; P<.001 and P=.002, respectively). In prespecified exploratory subgroup analyses, the superior survival benefit of temsirolimus was greatest for patients < 65 years and for those with elevated lactate dehydrogenase.[4] The most common all-grade toxicities (Table 2) for the temsirolimus group were managed with supportive measures. Fewer grade 3/4 AEs were seen with temsirolimus alone than with IFN-α or the combination (67% vs. 78% vs. 87%, respectively; P=.02). Most dose reductions or delays were reported for the combination group. Based on this study, in May 2007 temsirolimus received US Food and Drug Administration (FDA) approval for the treatment of advanced RCC.

This study included patients with both conventional and non-clear-cell histologies. Patients with histologies other than clear cell RCC accounted for 17% and 18% in the temsirolimus and interferon group, respectively. An unplanned secondary analysis for this patient subset was undertaken and suggested superior median OS and PFS for temsirolimus vs IFN-α with HR of 0.49 (95% CI, 0.29–0.85) and 0.38 (95% CI, 0.23–0.62), respectively.[48] While median OS was shorter in non-clear-cell histologies compared with conventional RCC, the benefit of temsirolimus appeared more pronounced with non-clear or indeterminate primary cell types. [48] This may be due to the fact that IFN has less efficacy in this group.[49]

Temsirolimus in 2nd-Line Setting

A randomized phase III trial has completed accrual (clinicaltrials.gov; NCT00474786), comparing temsirolimus with sorafenib in advanced RCC of any histology after progression on sunitinib, but no prospective 2nd-line data have been reported thus far. The largest retrospective series reported outcome for 87 patients treated at North American centers through the Torisel Compassionate Use Program.[50] The majority of patients had been pretreated with sunitinib (85%) or sorafenib (51%), 63% had pure clear-cell histology. The study population overall had unfavorable clinical features, mostly with either intermediate (53%) or poor (36%) MSKCC risk status[51]; 13% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 3. The reported OR was 5% (all PR); best

response of SD was 65%. The median TTP was 3.9; median OS was 11.2 months. Benefit was seen for both clear-cell and non-clear cell histologies.

EVEROLIMUS[1]

Phase I and II Studies

Everolimus (Afinitor®; Novartis, Basel, Switzerland) is a derivate of rapamycin, and unlike temsirolimus, is not converted to sirolimus in vivo. It has been studied as an immunosuppressant for solid organ transplantation. [52–54] Based on preclinical data with weekly treatment schedules,[55] a phase I trial determined safety for weekly dosing up to 70 mg and daily dosing up to 10 mg.[56] Clinical efficacy was seen for several RCC patients, including 1 confirmed partial response (PR), 1 unconfirmed PR, and 5 of 10 RCC patients progression-free at 6 months.[56] While pharmacodynamic profiling in this trial confirmed target inhibition for both dosing schedules, additional studies using a direct-link pharmacokinetic/pharmacodynamic model using tumor-bearing rats demonstrated more sustained S6K1 inhibition with daily rather than weekly everolimus.[57] Subsequently, a single-arm phase II trial enrolled 41 RCC patients with ≤ 1 prior regimen to be treated on everolimus 10 mg daily.[58] The trial reported a median PFS and OS of 11.2 and 22.1 months, respectively; ORR was 14%, and 70% of patients had either response or SD for ≥ 6 months.[58] Treatment was tolerated well with low-grade toxicities primarily managed with supportive care. The most common AEs included anorexia, nausea, diarrhea, stomatitis, and rash. Grade 3 pneumonitis (19%) was managed with dose delays and reductions. Four of the patients were successfully re-escalated to 10 mg.

Phase III Data

A multicenter, international, placebo-controlled phase III trial was conducted to investigate everolimus in the 2nd-line setting.[6] The RECORD-1 trial (*Re*nal Cell *C*ancer Treatment with *O*ral *R*ad001 given *d*aily) assigned 410 patients with advanced RCC to either everolimus 10 mg daily or placebo by 2:1 randomization, both in conjunction with best supportive care (Table 1). All subjects had clear cell RCC that had progressed on or within 6 months of therapy with VEGFR tyrosine kinase inhibitors (sunitinib, sorafenib, or both). The primary endpoint was PFS, and the trial was terminated after second interim analysis suggested that the study goal was met. The median duration of treatment was 95 days in the everolimus group, versus 57 days in the placebo group, and PFS was significantly longer for patients receiving study drug with HR of 0.3 (95% CI, 0.22–0.40; $P<.0001$). Median PFS was 4.0 and 1.9 months for everolimus and placebo, respectively. PFS benefit was maintained through various predefined subgroups, including MSKCC risk status, prior type of therapy (sunitinib vs sorafenib vs both), and demographic differences. Partial responses were seen in 1% of patients receiving everolimus, none with placebo. There was no significant difference in OS, likely due to the fact that 81% of all patients who progressed on placebo went on to receive everolimus.[6] The trial assessed health-related quality-of-life,[59,60] and failed to demonstrate significant time differences to outcome deterioration between the treatment and placebo groups. More toxicity was seen with everolimus, including higher rates of grade 3/4 AEs. Treatment discontinuation due to AEs was reported in 10% of patients receiving everolimus and 4% of patients in the placebo group.

Recently, updated efficacy and safety results of RECORD-1 were reported for 416 patients with mature OS data 13 months after interim analysis cutoff. [61] Median PFS for everolimus and placebo were 4.9 months and 1.9 months, respectively (HR, 0.33; 95% CI, 0.25–0.43; $P<.001$), with a 25% probability of remaining progression free after 10 months with everolimus. Again, benefit was seen in all MSKCC risk groups regardless of prior therapy. PR rates were 1.8% and 0%, respectively. A post hoc exploratory OS analysis used rank-

preserving structural failure time analysis estimates to correct for bias introduced by crossover from placebo to everolimus after progression, and thus provided an estimate of treatment effect per the original randomization. By this assessment, survival time with everolimus was estimated as1.9-fold longer than for placebo if no crossover occurred. The corrected OS for the placebo group was 10.0 months versus 14.8 months in the everolimus group.[61] Safety analysis was consistent with the original findings of the 2nd interim analysis (Table 2). Seven percent of the everolimus patients required dose modifications. Noninfectious pneumonitis was diagnosed in 14% (grade 3 in 4%) with a median time to onset of pneumonitis 108 days (range 24–257 days). Clinical and demographic factors were investigated as prognostics for both PFS and OS. Poor prognostic factors included prior treatment with sunitinib, MSKCC intermediate or poor risk status, elevated neutrophil or alkaline phosphatase levels, and metastases to liver or bone.[61]

Everolimus for Other Indications

The utility of using single-agent everolimus in the 1st–line setting is being investigated in the RECORD-3 trial, an international multicenter phase II trial randomizing treatment-naïve patients with advanced RCC to receive either the current standard of care, that is, 1st-line treatment with sunitinib followed by 2nd-line therapy with everolimus when disease progression is seen, vs the opposite (ie, everolimus followed by sunitinib), with a primary endpoint of PFS after 1st-line therapy.[62] The drug is also being studied in the neoadjuvant setting (clinicaltrials.gov: NCT01107509); lastly an adjuvant intergroup trial for locally advanced disease is in preparation.

COMBINATION THERAPY WITH OTHER TARGETED AGENTS

Concurrent treatment of RCC with mTOR inhibitors and other targeted agents has been studied in hopes of enhancing antitumor effects by parallel inhibition of multiple oncogenic signaling pathways. Unfortunately, this has been limited by treatment-associated toxicity. Several trials have evaluated the safety of combining an mTOR inhibitor with a VEGF TKI, which has typically required attenuated dosing schedules. In a phase I trial of sunitinib plus temsirolimus,[63] dose-limiting toxicities (DLTs) were seen in 2 of 3 patients at the starting dose of temsirolimus 15 mg weekly and sunitinib 25 mg daily (1 grade 3 acneiform rash, 1 grade 3 cellulitis). Other AEs included hemorrhage, thrombocytopenia, gastrointestinal toxicity, and severe infection. Because of efficacy concerns at lower doses, the study was terminated early.[63] The combination of sunitinib and everolimus proved toxic in a separate phase I trial,[64] and investigators switched to a weekly schedule of everolimus, as 2 of 2 patients suffered DLT even at attenuated doses of sunitinib 37.5 mg and everolimus 5 mg. Even so, chronic treatment was only tolerable at the lowest weekly dosing schedule of everolimus 20 mg weekly, with sunitinib 37.5 mg daily (4 weeks on, 2 weeks off). DLTs included mucositis, vomiting and leukopenia. Five patients (25%) achieved PR, 3 of these had non-clear-cell RCC.[64]

In a phase I trial of sorafenib plus temsirolimus in advanced solid tumors, investigators reported 9 DLT in 23 patients treated up to a level of temsirolimus 25 mg weekly and sorafenib 400 mg twice daily. Toxicities were predominantly mucocutaneous, but also included thrombocytopenia and loss in renal function.[65] Sorafenib was better tolerated when combined with everolimus, as per preliminary reports of another dose-finding study.[66] Still, 2 out of 4 patients in the second cohort suffered DLT (grade 4 uricemia and grade 3 elevation in lipase with concurrent pancreatitis, respectively) with everolimus 5 mg daily plus sorafenib 400 mg twice daily. Three of 10 evaluable patients achieved PR, 2 had SD, 5 showed evidence of progression.

The combination of temsirolimus and tivozanib, a novel VEGFR TKI, appears to be better tolerated per recent reports of an ongoing phase I study in pretreated RCC patients.[67] Better tolerance was also seen for combinations with bevacizumab. A phase I/II trial of temsirolimus and bevacizumab[68] established safety at standard doses (temsirolimus 25 mg IV weekly, bevacizumab 10 mg/kg IV every 2 weeks) with 1 DLT in 6 patients (grade 3 mucositis). The tolerability at full doses[68] prompted ongoing randomized studies. In the phase III INTORACT (Investigation of Torisel and Avastin Combination Therapy) trial, targeting accrual of ~800 subjects, treatment-naïve patients are randomized to receive bevacizumab plus temsirolimus versus bevacizumab plus IFN-α (clinicaltrials.gov; NCT00631371). Similarly, the TORAVA (TORisel and AVAstin) phase II trial is comparing bevacizumab plus temsirolimus vs single-agent sunitinib vs bevacizumab plus IFN-α in the 1st-line setting. Preliminary findings have been presented;[69] and revealed higher drop-out rates but no improvement in efficacy for the combination over the 2 control arms. The ECOG BeST (Bevacizumab Sorafenib Temsirolimus) is an ongoing 4-arm phase II trial of bevacizumab/temsirolimus vs bevacizumab/sorafenib vs sorafenib/temsirolimus vs sorafenib alone (clinicaltrials.gov; NCT00378703).

The combination of everolimus and bevacizumab is tolerated at full doses as demonstrated in a phase I trial that reported DLT and grade 1–2 toxicities.[70] A subsequent phase II study in pretreated advanced RCC[71] yielded an ORR of 30% and 23% with median PFS of 9.1 months and 7.1 month in the un-and pretreated groups, respectively. The study aim of raising PFS rate from 50% (phase II data for single-agent bevacizumab in pretreated patients) to 70% was met at 5 months. Median PFS and OS were reported at 9.1 and 21.3 months for untreated patients, 7.1 and 14.5 months for the pretreated group, respectively.[72] The most common grade 3/4 toxicities included proteinuria (26%), mucositis (15%), fatigue (12%), and diarrhea (9%). The final PFS findings for this trial are not superior to that reported in the 1st-line setting for phase III studies of bevacizumab + IFN-α.[5,73] The latter is currently being addressed in the phase II RECORD-2 trial comparing bevacizumab + everolimus to bevacizumab + IFN-α in untreated clear cell RCC.[74] Similarly, the Cancer and Leukemia Group B (CALGB) is conducting a phase III trial randomizing patients to receive everolimus plus bevacizumab vs placebo after progression on VEGF TKI (clinicaltrials.gov; NCT01198158).

INCIDENCE AND MANAGEMENT OF AEs SPECIFIC TO MTORC1 INHIBITORS

Several class-specific effects, primarily metabolic and pulmonary toxicities, have occurred with rapamycin and its analogues, and require close attention while treating patients with these agents.[75]

The attenuating effects of the PI3K/Akt/mTOR cascade on insulin signaling has been established,[76,77] and mTOR has been implicated in insulin resistance.[78] Expectedly, clinical trials of temsirolimus and everolimus have noted AEs on glucose metabolism. The ARCC trial reported hyperglycemia in 26% of patients.[4] Investigators attributed hyperglycemia to study drug in 18% (all grades) and 9% (grades 3 or 4) of subjects.[79] RECORD-1[61] reported hyperglycemia in 57% of patients receiving everolimus, grade 3 or 4 glucose intolerance in 15%. There are no official recommendations guiding management of treatment associated hyperglycemia. Instead, physicians should adhere to good clinical practice, which includes adequate glucose control before initiation of mTOR directed treatment, education of patients on the symptoms of hyperglycemia, and intermittent monitoring of fasting glucose levels. Laboratory testing, interpretation of levels, and management should mirror that of type 2 diabetes mellitus.[75,80,81]

Effects of lipid metabolism can be explained through the roles of mTOR in cell metabolism.[11] In the phase III trial leading to its registration, temsirolimus caused hypercholesterolemia and hypertriglyceridemia in 21% and 25% of patients, respectively, primarily grade 1–2.[79] The reported incidence was higher for everolimus; cholesterol and triglycerides were elevated in 77% and 73% of patients treated with drug on the pivotal trial, respectively (the majority grade 1–2). As for the management of hyperglycemia, no standardized guidance has been issued for rapalogues-induced hyperlipidemia. Most investigators have adapted target levels and management of abnormally high levels from general medical practice [82]. Prescribing physicians should ascertain adequate levels prior to starting treatments, and monitor patients for development of hyperlipidemia.

Mild hypophosphatemia has been reported in 6% with temsirolimus and 37% for everolimus in phase III trials.[6,79] Severely low levels can impair neurologic and myocardial function and should be replenished.

Much attention has been given to nonspecific interstitial pneumonitis, which has been associated with the use of mTOR inhibitors. While this is often asymptomatic or presents with mild dyspnea and/or cough, it can be life-threatening in extent. In severe cases, systemic corticosteroids have been found to be beneficial. The original design of the ARCC trial paid limited attention to nonspecific interstitial pneumonitis, [4] however, a subsequent independent, blinded review of 178 patients in the temsirolimus group revealed drug-induced pneumonitis in 29% (vs 6% of 138 in the IFN-α group; $P<.0001$).[83] Most (60%) occurred within the first 8 weeks of treatment; only 31% were symptomatic. The incidence of noninfectious pneumonitis on RECORD-1 was 13.5% (3.6% grade 3, none grade 4)with a median time to occurrence of 108 days.[61] Forty-three percent of symptomatic patients received corticosteroids, 54% underwent dose-modification of study drug, 27% of cases discontinued treatment permanently. Clinical pneumonitis was fully reversible in 54% of cases. This trial contained a prospective, independent monitoring of patients for pneumonitis that was reported separately.[84] On blinded review of serial images obtained with the study, baseline radiographic abnormalities were present in 17% of all patients, in 24% of those who went on to develop clinical pneumonitis, and in 50% of those with subsequent grade 3 pneumonitis. New or worsening radiographic changes suggestive of pneumonitis were detected in 53.9% of patients on everolimus, which included 38.9% of patients without clinical suspicion for pneumonitis. All patients had undergone pulmonary function tests at baseline, which did not help predict likelihood of developing clinical pneumonitis. Chest X-rays were found to be less sensitive than CT scans in detecting abnormalities in asymptomatic patients or confirming clinical pneumonitis by radiographic changes. Based on their observations, the authors issued specific management guidelines (Table 3).[84]

Other potentially class-related toxicities have been recognized but were not reported with the registration trials. These include increased risk of angioedema with angiotensin-converting enzyme (ACE) inhibitors [85] and rapalogues-associated enteritis.[86]

MECHANISMS OF RESISTANCE

While clinical studies have proven efficacy for rapalogues in advanced RCC, patients eventually acquire resistance to therapy. Preclinical models and experiments using patient tumor samples have suggested that TORC1 inhibitors activate Akt and its downstream substrates through a feedback loop involving the insulin-like growth factor I receptor (IGF-IR).[87–90] Active mTOR signaling promotes receptor dissociation and protein degradation of IRS-1, an effect mitigated by inhibition of mTORC1. Such inhibition leads to enhanced IGF-1 signaling.[88] This is mediated through the mTORC1 downstream effector S6K and requires PI3K function, but was found to be independent of TSC-2.[87,90,91] These findings

propose the following mechanism: inhibition of mTORC1, through decreased activity of S6K, stabilizes IRS-1 association with its receptor, leading to activation of PI3K and subsequent phosphorylation of Akt (T^{308}).

A different mechanism of resistance to mTORC1 inhibition relates to the equilibrium between mTORC1 and mTORC2 signaling,[92,93] which shifts toward mTORC2 in treatment with rapalogues, subsequently leading to Akt (S^{473}) phosphorylation and activation.[94] Preclinical studies in Non-Hodgkins lymphoma have confirmed such rapamycin induced, mTORC2 mediated activation of Akt and demonstrated this effect to be independent of PI3K signaling.[95].

A third proposed mechanism of resistance involves a negative feedback loop with a separate signaling pathway. Data from a small number of patients receiving everolimus for breast cancer, melanoma, and colorectal cancer suggested that such treatment can activate the mitogenactivated protein kinase (MAPK) signaling cascade, a separate well established oncogenic pathway.[96] MAPK feedback activation was found to be PI3K-dependent.[96]

Current drug development incorporates an understanding of these mechanisms, and ongoing efforts include strategies for combined inhibition of mTORC1 and PI3K, mTORC1 and 2, as well as PI3K/mTOR and MAPK.

FUTURE DIRECTIONS

Study of temsirolimus and everolimus continues. Both drugs are being tested in combination with other targeted agents and outside of there currently approved indication for advanced RCC. Considering the potential mechanisms of resistance to rapalogues, several novel agents targeting PI3K/Akt/mTOR are being developed for anticancer therapy in early phase clinical trials.[97,98] These include PI3K inhibitors (eg, CAL-101, BKM-120, XL-147), Akt inhibitors (eg, MK-2206, Perifosine), mTORC1 inhibitors (eg, ridaforolimus), ATP-competitive inhibitors of the mTOR kinase domain that target both mTORC1 and mTORC2 (eg, PP242, Torin-1), as well as combined PI3K/mTORC1/mTORC2 inhibitors (eg, BEZ235, XL765, GDC0980).

Several biomarkers have been tested for prognostic value, particularly their potential to predict response to RCC treatment with mTOR inhibitors. Hyperactivation of the PI3K/Akt/mTOR pathway assessed by immunohistochemistry on 375 RCC nephrectomy specimens adversely affected outcome, independent of stage.[29] Tumor tissue from >50% of patients in the ARCC trial [4] was tested for baseline PTEN and HIF1α levels, but no correlation with treatment benefit for temsirolimus was seen.[99] A smaller study investigated PI3K/Akt/mTOR pathway in 20 RCC patients treated with temsirolimus, and suggested that pS6K levels and possibly pAkt can help predict response to temsirolimus.[100] Mutation analysis in preclinical models and a small series of patients with various solid tumors have shown that deregulation of phosphoinositide-3-kinase catalytic α peptide (*PIK3CA*) and *KRAS* can attenuate response to everolimus.[101] Importantly, this report did not include RCC patients, and mutations in *PIK3CA* or *KRAS* are uncommon in RCC.[102–105]

Identification of new, more effective agents is one of the major goals for the coming years. The other will be to apply our growing understanding of the molecular changes behind pathogenesis and treatment resistance successfully to optimize drug selection for individual patients.

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Table 1

Trial design and treatment efficacy of mTOR inhibitors in phase III trials in advanced RCC

	ARCC trial[4]	RECORD 1 trial[6,61]
No. of Pts	626	416
Histologies	All	Clear cell RCC component
Prior therapy	None	Sunitinib, sorafenib or both
Clinical risk	All with ≥ 3/6 poor-risk features: LDH ≥ 1.5 × ULN decreased Hgb corrected Ca of ≥ 10 mg/dL time diagnosis to treatment initiation of <1 year KPS 60%–70% ≥ 2 metastatic sites	Favorable Risk[a] 29% Intermediate Risk[a] 57% Poor Risk[a] 15% (well balanced between groups)
Randomization arms, No. of Pts	IFN: 207 Tem: 209 IFN/Tem: 210	Everolimus: 277 Placebo: 139
Primary endpoint	OS	PFS

RESULTS

Responses	1st-Line Tem	1st-Line IFN	2nd-line Everolimus	2nd-Line Placebo
mPFS (mos)	3.8 (CI 3.6–5.2)[b]	1.9 (CI 1.9–2.2)	4.9 (CI 4.0–5.5)[c]	1.9 (CI 1.8–1.9)[c]
mOS (mos)	10.9 (CI 8.6–12.7)[d]	7.3 (CI 6.1–8.8)[d]	14.8 [e]	14.4[f]
Response	ORR: 9% (CI 4.8–12.4) Benefit:[g] 32% (CI 25.7–38.4)	ORR: 5% (CI 1.9–7.8) Benefit:[g] 16% (CI 10.5–20.4)	Best response: PR: 2% SD: 67% (CI not reported)	Best response: PR: 0% SD: 32% (CI not reported)

[a] risk stratification per MSKCC clinical risk score [47]

[b] HR not reported

[c] HR: 0.33; CI 0.25–0.43; $P<.001$

[d] HR: 0.73; CI 0.58–0.92; $P=.008$

[e] HR: 0.87; CI 0.65–1.15; $P=.16$

[f] Rank preserving structural failure time approach estimated true mOS for placebo group to be 10.0 months;

[g] clinical benefit defined as ORR or SD x ≥ 24 weeks

Abbreviations: IFN, interferon-α; Tem, temsirolimus; LDH, lactate dehydrogenase; ULN, upper limit of normal; Hgb, hemoglobin; Ca, Serum Calcium; KPS, Karnofsky performance status; mOS, median overall survival; mPFS, median progression-free survival; CI, 95% confidence interval; HR, hazard ratio; ORR, objective response rate; PR, partial remission; SD, stable disease; mLOT, median length of treatment; OS, overall survival; PFS, progression free survival

Table 2

Adverse events in phase III trials of mTOR inhibitors in advanced RCC

	1st-Line Temsirolimus in Poor-risk Pts [4]		2nd-Line Everolimus after Prior VEGF TKI [61]	
Adverse Events	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Asthenia	51	11	33	3–4
Fatigue	NR		31	5
Rash	47	4	29	1
Nausea	37	2	26	1
Anorexia	32	3	25	1
Pain	28	5	NR	
Dyspnea	28	9	24	7
Infection	27	5	37	7
Diarrhea	27	1	30	1
Constipation	20	0	NR	
Peripheral edema	27	2	24	<1
Cough	26	1	30	<1
Dyspnea	NR		24	7
Pneumonitis[1]	NR		14[1]	4[1]
Fever	24	1	20	<1
Abdominal Pain	21	4	NR	
Stomatitis	20	1	44	4–5
Vomiting	19	2	20	2
Headache	15	1	19	0–2
Epistaxis	NR		18	0
Pruritus	NR		14	<1
Dysgeusia	NR		10	0
Laboratory Abnormalities				
Anemia	45	20	92	13
Thrombocytopenia	14	1	23	1
Lymphopenia	NR		51	16

	1st-Line Temsirolimus in Poor-risk Pts [4]		2nd-Line Everolimus after Prior VEGF TKI [61]	
Adverse Events	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Neutropenia	7	3	14	<1
Increased Creatinine	14	3	50	1
Hyperlipidemia	27	3	73	<1
Hypercholesterolemia	24	1	77	4
Hyperglycemia	26	11	57	15–16
Increased AST	8	1	25	0–2
Hypophosphatemia	NR		37	6

[1] Includes interstitial lung disease, lung infiltration, pneumonitis, pulmonary alveolar hemorrhage, alveolitis, and pulmonary toxicity

Abbreviations: VEGF, vascular endothelial growth factor; TKI, tyrosine kinase inhibitor; NR, not reported; AST, aspartate amino-transaminase

Table 3

Management of everolimus-associated noninfectious pneumonitis[84]

Severity	Definition	Intervention	Imaging / Further Diagnostic Workup
Grade 1	Radiographic changes with few or no symptoms	• Continue without dose adjustment, maintain close clinical follow-up.[1]	• Obtain CT chest, PFT • Repeat CT or CXR every 2 cycles until back to baseline
Grade 2	Moderate symptoms	• Reduce dose to 5 mg/d until ≤ grade 1 • Consider interruption if symptoms troublesome to Pt • D/C treatment if no improvement in ≥ 3 weeks • Consider corticosteroid, if above is ineffective[2]	• Obtain CT chest, PFT • Repeat every cycle until return to baseline. • In appropriate clinical setting, rule out etiologies, such as infection (bronchoscopy), PE, orcardiac etiology.
Grade 3	Severe symptoms	• Interrupt everolimus until ≤ grade 1 • Initiate corticosteroids[3] – high-dose IV methylprednisolone for respiratory distress – lower dose in less severe cases • Upon resolution of toxicity, consider re-initiating everolimus at attenuated dose	• Obtain CT chest, PFT • Repeat every cycle until return to baseline • Bronchoscopy • Consider workup for other etiologies (eg, PE, cardiac)
Grade 4	Life-threatening	• D/C everolimus permanently • Initiate corticosteroids [3] • Do not restart	• Obtain CT chest, PFT • Repeat every cycle until return to baseline • Bronchoscopy • Consider workup for other etiologies (eg, PE, cardiac)

Adapted from White et al. *Am J Respir Crit Care Med* 2009.

Abbreviations: CT, computed tomography; CXR, chest X-ray; PFT, pulmonary function test; PE, pulmonary embolism

[1] Except if findings extensive or baseline pneumonitis worsening. In either case consider interruption / dose modification.

[2] Prior to initiation of corticosteroids, exclude infectious process, cardiac etiology or pulmonary embolism, if appropriate

[3] Infectious etiology or pulmonary embolism should be excluded if either suggested by clinical presentation; however, this should NOT delay initiation of steroids.