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Novel Targeting of Phoshatidylinositol-3 Kinase and Mammalian Target of Rapamycin (mTOR) in Renal Cell Carcinoma

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Abstract

Allosteric inhibitors of the kinase mammalian target of rapamycin (mTOR) have demonstrated significant clinical activity in patients with advanced renal cell carcinoma (RCC). Unfortunately, substantial clinical responses to these rapalogues are only seen in a subset of patients with advanced RCC. Preclinical studies have identified multiple theoretical shortcomings of the rapalogues and numerous novel agents directed against the PI3-K/Akt/mTOR pathway which address many of these shortcomings are in active clinical development. In this review, we will discuss the preclinical and clinical experience with the rapalogues in RCC, potential mechanisms of resistance to the rapalogues, and the progress in the clinical development of novel agents directed against the PI3-K/Akt/mTOR Pathway.

Keywords

Renal Cancer; PI3-Kinase; Akt; mTOR; TORC1; TORC2; HIF

Introduction

The therapeutic relevance of the signaling pathway regulated by mammalian target of rapamycin (mTOR) in renal cell carcinoma (RCC) has been established by the clinical efficacy of allosteric inhibitors of this kinase. Two such rapalogues, temsirolimus and everolimus, are now approved by the United States Food and Drug Administration (FDA) for the treatment of patients with advanced RCC (1, 2). Unfortunately, significant clinical responses to these agents are only experienced by a subset of patients. Not surprisingly, developing predictive models to identify this subset of patients prior to treatment has been a priority for RCC researchers. At the same time, much effort has been committed to developing more effective therapies targeting this signaling pathway including therapies aimed at targets upstream of mTOR such as phophatidylinositol 3-kinasee (PI3-K) and Akt (Protein Kinase B). In this article, we will review the scientific rationale for mTOR as a therapeutic target, clinical data with current rapalogues, the scientific rationale for novel therapeutic approaches, novel agents in development, preclinical studies with these novel agents, and the clinical experience thus far.

Rationale for mTOR as a Therapeutic Target

mTOR exists in two functionally distinct complexes which are distinguished by their relative sensitivity to rapamycin. TORC1, a complex including Raptor (Regulatory associated protein of TOR), is sensitive to rapamcyin, while TORC2, a complex including Rictor (Rapamycin insensitive companion of TOR) is relatively resistant to rapamcyin. TORC2 appears to function as part of the PI3-K pathway and activates Akt (through

phosphorylation of the Ser473 residue) and serum- and glucocorticoid-regulated kinase 1 (SGK1). TORC1 appears to regulate the majority of functions which have been canonically associated with mTOR and acts through its downstream effectors, the p70 S6 Kinase (S6K) and the eukaryotic initiation factor 4E binding proteins (4E-BP1 and 4E-BP2), to regulate protein synthesis and cap-dependent translation. TORC1 directly phosphorylates S6K to activate ribosomal biosynthesis. The phosphorylation of the 4E-BPs by TORC1 causes them to disassociate from their binding partner, eIF4E and thereby liberating it to interact with the 5′UTR of capped mRNA and initiate cap-dependent translation. While the p70RSK and the 4E-BPs have traditionally been thought of as the primary TORC1 substrates, additional substrates are emerging. Recently, the adapter protein growth factor receptor bound protein 10 (Grb10) has been described as a major substrate of TORC1 and shown to act as a negative regulator of PI3-K through direct interation with insulin response substrate 1 (IRS1) (3).

The therapeutic efficacy of the rapalogues in RCC was discovered largely serendipitously through clinical investigation, prompting many subsequent investigations exploring the possible mechanisms for the observed clinical effect. Many initial hypotheses surrounded the effect of the rapalogues on the expression of hypoxia inducible factors (HIF) -1 and -2. The inappropriate accumulation of HIF-1α and HIF-2α as a result of bi-allelic alterations in the von Hippel Lindau (*VHL*) gene has been shown to be a major step in tumorigenesis of the majority of clear cell RCC (4, 5). Following studies suggesting that mTOR activation may increase *HIF-1α* gene expression, both at the levels of messenger RNA (mRNA) translation and protein stabilization, many investigators proposed that the attenuation of HIF-1α expression might underlie the efficacy of the rapalogues in RCC (6, 7).

Many recent findings, however, cast some doubt upon this possibility. First, while the overlap between the roles of HIF-1α and HIF-2α are poorly understood, it is generally accepted that HIF-2α is the more relevant HIF with respect to the development and progression of RCC (8, 9). In fact, recent studies suggest that HIF-1α may function as a tumor suppressor in clear cell RCC (10). Another recent study segregating *VHL* deficient sporadic RCC into two subtypes, those expressing both HIF-1α and HIF-2α and those expressing HIF-2α alone, found no specimens expressing HIF-1α alone (11). Secondly, it has been suggested that the expression of HIF-1α is dependent upon the activity of both TORC1 and TORC2, while the expression of HIF-2α is dependent upon TORC2 activity alone (12). As TORC2 activity is felt to be relatively resistant to inhibition by the rapalogues, the hypothesis that the mechanism of action of the rapaloges in RCC may be mediated by attenuation of HIF activity must be considered far from proven.

An alternative possibility remains that the rapalogues may attenuate the translation of critical mRNA in RCC. Although the translation of all capped mRNAs depends on the availability and activity of eIF4E, the translation of certain transcripts, in particular those with complicated 5′ UTR containing stem loop structures, is especially eIF4E-dependent and therefore highly susceptible to the suppressive effects of TORC1 inhibitors (13). This group of difficult to translate mRNAs includes the transcripts of several genes relevant to cell cycle progression and transformation such as *cyclin D*, *VEGF*, *survivin*, and *c-myc*. The suppression of the expression of these gene products may therefore be a primary mode of efficacy of the rapalogues in RCC.

Clinical Data with Rapalogues

While the mechanism of action of the rapalogues in RCC remains unclear, the clinical efficacy of these agents is well established and both temsirolimus and everolimus have demonstrated clinical efficacy in large randomized phase III trials in patients with advanced

RCC. Temsirolimus is an intravenously administered analog of rapamycin. After showing promising activity in a phase II trial randomizing patients with metastatic RCC to three different doses (14), temsirolimus was assessed in a randomized three-arm Phase 3 trial comparing temsirolimus alone versus IFN-α alone versus the combination (1). As the phase II study suggested potentially unique efficacy in patients with poor prognostic features in a retrospective analysis, the phase III study enrolled only patients with metastatic RCC and ≥3 of 6 risk factors; (5 MSKCC risk factors [Karnofsky PS < 80; time from diagnosis to randomization < 12 months; serum LDH > 1.5 ULN; hemoglobin < LLN; corrected serum calcium > 10mg/dl] + >1 metastatic site). Overall, 626 previously untreated patients were enrolled and randomized in a 1:1:1 fashion to receive IFN-α alone (3 million Units three times weekly), temsirolimus (25 mg IV weekly), alone, or the combination (temsirolimus 15 mg weekly and 6 million Units IFN-α three times weekly). The overall survival of patients treated with temsirolimus alone was statistically longer than those treated with IFN-α alone (7.3 versus 10.9 months; 0.73 hazard ratio, p=0.0069). There was no statistical difference between patients treated with IFN-α alone and the combination of IFN-α and temsirolimus. Based on these findings, temsirolimus was approved by the FDA for therapy in advanced RCC on May 30, 2007 and is now considered a standard therapeutic option in the first-line setting for patients with poor prognosis features.

Everolimus is an orally administered rapalouge and was assessed in a randomized, double-blind, placebo-controlled phase III in patients with advanced RCC who had failed prior treatment with either sorafenib, sunitinib, or both within the preceding 6 months (**RE**nal Cell cancer treatment with **O**ral **R**AD001 given **D**aily-1 [RECORD-1]) (2). Overall, 416 patients were enrolled and randomized in a 2:1 fashion to receive either everolimus (n=277) or placebo (n=139) each together with best supportive care. The primary endpoint was PFS and randomization was unblinded at time of progression and patients on placebo were allowed to crossover to open-label everolimus. At the final central radiology assessment the median PFS for patients treated with everolimus was 4.88 months as compared with 1.87 months in the placebo group (hazard ratio 0.33, [95% CI 0.25–0.43] p < 0.0001) (15). Based on these findings, everolimus was approved the FDA in March, 2009 for the treatment of patients with advanced RCC who failed either sorafenib, sunitinib or both and is now considered a standard second-line therapeutic option following the failure of VEGF-targeted TKI.

Mechanism of Resistance to Rapalogues in RCC

Despite the clear activity of the rapalogues in RCC, it must be noted that substantial antitumor responses are limited to a subset of patients treated with these agents. Therefore, much effort has been directed at identifying possible mechanisms of resistance to these agents. Perhaps the most well described shortcoming of the rapalogues are their potential to induce the feedback activation of PI3-K and Akt. Many investigators have shown that treatment with rapamycin can result in the upstream activation of both PI3-K though a feedback loop involving the IGF-1 receptor and Akt through derepression of TORC2 resulting in TORC2-mediated phosphorylation of Akt on Ser473 (16, 17). PI3-K/Akt signaling activates an array of kinases, transcription factors and other proteins besides mTOR which promote cell growth and survival (18, 19). These prosurvival effects include the phosphorylation and nuclear export of FOXO3a, which reduces the expression of fas ligand, Bim, and other pro-apoptotic proteins. PI3-kinase activation also results in the downstream activation of NF-κB and the inactivation of pro-apoptotic proteins such as BAD and procaspase 9. Activation of any of these pro-survival signals may have effects which counteract the antitumor activity of the rapalogues. Finally, the feedback activation of PI3-K may also directly undermine the efficacy of rapalogues by promoting the phosphorylation of eIF4E by Mnk1, thereby enhancing its affinity for the mRNA cap structure and activating cap-dependent translation (20).

Many investigators have also implicated the relatively limited efficacy of the rapalogues against entire array of mTOR-regulated functions. As noted earlier, the kinase activity of mTOR in TORC2 is felt to be relatively resistant to the effects of rapalogues. This may be particularly relevant in the largely HIF-2α driven clear cell RCC given the aforementioned dependence of HIF-2α expression on TORC2 activity. Furthermore, it is becoming increasingly clear that the phosphoryation of the 4E-BP's are less responsive to rapalogues than that of S6K and S6 Ribosomal protein and the suppression of 4E-BP1 phosphorylation by rapamycin can be reversed within a few hours of drug exposure (21, 22). Therefore, the attenuation of cap-dependent translation of critical mRNA, proposed to be a major mechanism of the anti-tumor effect of rapalogues, may only be a transient event.

Drugs in Development

Not surprisingly, many of the novel agents targeting the PI3-K/Akt/mTOR axis directly address some of the proposed shortcomings of the rapalogues. Some the earliest agents to enter clinical assessment have been pan-isoform inhibitors of PI3-K. These agents are direct inhibitors of the kinase activity of the p110α catalytic subunit of Class IA PI3-Ks that act as ATP mimetics, binding competitively and reversibly to the p110 ATP-binding pocket. As PI3-K/Akt is a major activator of mTOR kinase activity, inhibition of PI3-K would be expected to attenuate mTOR activity in a majority of cancer types in a manner which may be free of the aforementioned feedback loops. Several such agents in active clinical development are noted in Table 1.

The activity of TORC1, however, responds to many inputs other than PI3-K/Akt signaling and can be activated independently of PI3-K/Akt signaling through multiple mechanisms including through the liver kinase B1 (LKB1) – monophophate activated protein kinase (AMP-K) pathway and the mitogen activating protein kinase (MAP-K) pathway (23, 24). TORC1 can also be activated in response to amino acid availability in a manner which is independent of tuberous sclerosis complex (TSC) 1 and 2 at the lysosomal membrane through the RAG-GTPases (25). Therefore, there may be some cancers in which the inhibition of PI3-K does not reliably result in the downstream inhibition of mTOR activity. For that reason, there may be additional benefit to inhibiting both PI3-K and mTOR simultaneously. Structural similarities between the ATP-binding domain of p110α subunit of PI3-K and the catalytic domain of mTOR have led to the development of a class of agents that are both pan-isoform inhibitors of PI3-K and mTOR. Unlike the currently available rapalogues, these agents are active site inhibitors of mTOR and have the theoretical advantage of inhibiting the kinase activity of mTOR regardless of whether it is in complex with raptor (TORC1) or rictor (TORC2). Several dual PI3-K/mTOR inhibitors in active clinical development are listed in Table 1. A few of these agents such as GDC-0980 and BEZ235 have entered phase II clinical trials in renal cell carcinoma specifically.

Additional agents in active clinical development include active site inhibitors of mTOR alone, isoform-specific PI3-K inhibitors, and inhibitors of Akt. The active site inhibitors of mTOR inhibit the kinase function of both TORC1 and TORC2 while sparing PI3-K. The primary theoretical advantage of the isoform-specific PI3-K inhibitors is that they may have more focused toxicities compared with the pan-isoform inhibitors, allowing these agents to be tolerated at doses, which can result in more complete and reliable inhibition of kinase activity. Thus far, however, no particular PI3-K isoform has been implicated as more relevant in RCC and the utility of the isoform-specific agents in this disease remains to be seen. Like the PI3-K inhibitors, Akt inhibitors are slowly advancing through clinical assessment. Amongst the inhibitors in clinical development are both allosteric inhibitors such as MK2206 and ATP-competitive catalytic inhibitors such as GSK690693 and GDC-0941. These agents thus far are all pan-isoform inhibitors of Akt.

Preclinical Data

Preclinical studies with PI3-Kinase inhibitors in RCC have supported the hypothesis that these agents may have activity in RCC. Inhibition of PI3-K/Akt signaling by PI3-K inhibitors LY294002 and wortmannin resulted in significant reduction in cell proliferation and induction of tumor cell apoptosis by both TUNEL and propidium iodide staining in RCC cell lines (786–0) (26). Treatment of nude mice bearing RCC xenografts derived from the 786-O cells with LY294002 resulted in up to 50% reduction in tumor size. We have also observed that treatment of nude beige mice bearing RCC xenografts with BEZ235, a dual inhibitor of PI3-K/mTOR, resulted in significantly greater suppression of tumor growth compared with either rapamycin or vehicle (27). This suppression of tumor growth was correlated with reduced markers of proliferation (Ki67 staining) and modest induction of markers of apoptosis (cleaved caspase 3 staining). In support of the hypothesis that a dual inhibitor of PI3-K/mTOR may more effectively suppress both the cap-dependent translation of critical mRNA and TORC2 activity, the superior antitumor activity of BEZ235 in the RCC xenografts was associated with suppression of cyclin D1 and HIF-2α expression compared with both vehicle and rapamycin. These pre-clinical data provides the rationale for the clinical assessment of novel agents targeting the PI3-K/Akt/mTOR pathway in RCC.

Clinical Data

One of the earliest such agents to be assessed in RCC was perifosine, an orally available alkylphospholipid which prevents Akt activation by blocking its pleckstrin-homology domain dependent recruitment to the cell membrane. Perifosine was recently assessed in two independent phase II trials in patients with advanced RCC who had failed prior targeted therapy (28). In Perifosine 228, 24 patients with advanced RCC who had progressed after prior therapy with VEGF-targeted agents and/or cytokines were enrolled and treated with perifosine at 100mg once daily. In Perifosine 231, 50 patients with advanced RCC were enrolled into two groups and treated with perifosine at a dose of 100mg once daily. Group A included patients who failed a VEGFR TKI but not on an mTOR inhibitor; whereas Group B included patients who failed both targeted agents. In the combined analysis of 74 patients on both trials, 6 patients experienced a partial response (ORR 8%) and the median PFS was 14 weeks [95% CI (12.8, 20.0)]. The most common toxicities were fatigue, musculoskeletal pain, diarrhea and nausea. Although perifosine had clear clinical activity in RCC, it was felt that this activity was not superior to currently available agents and this agent was not worthy of further development as a single-agent in RCC.

The lack of robust clinical activity seen with perifosine has not dampened the enthusiasm for PI3-K/Akt as a therapeutic target in RCC, however. Perifosine is an indirect inhibitor of Akt. As mentioned earlier, more reliable inhibition of this pathway may be achieved with the catalytic inhibitors of PI3-K/mTOR or with direct inhibitors of Akt (both catalytic and allosteric). Not surprinsingly, several clinical trials with novel inhibitors of PI3-K/mTOR and Akt are underway as shown in Table 2. It is hoped that the results from these clinical trials may provide further validation of the PI3-K/Akt pathway as a therapeutic target in RCC.

Conclusion

TORC1 is a validated therapeutic target in patients with advanced RCC. Substantial scientific rationale exists to assess novel inhibitors of PI3-K and Akt in patients with renal cell carcinoma and these agents are now advancing in clinical development. Parallel with these efforts will be those directed at identifying predictive biomarkers of response to agents targeting the PI3-K/Akt/mTOR pathway. Exciting progress has been made in this respect

with the recent mutational analysis reported by Voss *et al* suggesting that the tumor specimens from a subset of robust responders to rapalogues may frequently possess mutations resulting in constitutive activation of mTOR (29). This, together with data emerging from The Cancer Genome Atlas (TCGA) Project regarding the frequency of mutations in the PI3-K/Akt/mTOR pathway in RCC, enhances the expectation that genetic predictors of response to agents targeting this pathway may soon be identified. It is hoped that the combination of improved patients selection strategies and potentially more effective agents will lead in improvements in the therapeutic index of agents directed against this critical pathway.

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Table 1

PI3-K/Akt/mTOR Inhibitors in Clinical Development

Agent	Company	Stage of Clinical Development
Pan-Isoform PI3-K Inhibitors		
SAR245408 (XL147)	Sanofi/Adventis, Exelixis	Phase I, II
BKM120	Novartis	Phase II, III
GDC-0941	Genentech	Phase I, II
BAY 80–6946	Bayer	Phase I
GSK1059615	GlaxoSmithKline	Phase I
ZSTK474	Zenyaku	Phase I
PI3-K/mTOR Inhibitors		
SAR254409 (XL765)	Sanofi/Adventis, Exelixis	Phase I, II
BEZ235	Novartis	Phase I, II
GDC-0980	Genentech	Phase I, II
GSK1059615	GlaxoSmithKline	Phase I
PF-04691502	Pfizer	Phase I
PKI-587	Pfizer	Phase I
PWT33597	Pathway Therapeutics	Phase I
Active Site mTOR Inhibitors		
MLN0128	Millenium, Intellikine	Phase I
OSI-027	Astellas	Phase I
AZD8055	AstraZeneca	Phase I
Isoform-Specific PI3-K Inhibitors		
BYL719 (alpha specific)	Novartis	Phase I
INK1117 (alpha specific	Intellikine/Millenium	Phase I
SAR260301 (beta specific)	Sanofi-Adventis	Phase I
TGR-1202 (delta specific)	TG Therapeutics	Phase I
GS-1101 (delta specific)	Gilead	Phase II-III
AS-252424 (upsilon specific)	Merck Serono	Pre-clinical
Akt Inhibitors		
GDC-0068	Genentech	Phase I, II
MK2206 (allosteric inhibitor)	Merck	Phase I, II
GSK690693	GlaxoSmithKline	Phase I, II

Table 2

Ongoing Trials with Novel PI3-K/Akt Inhibitors in RCC

Agent	Mechanism of Action	Trial
MK2206	Allosteric inhibitor of Akt	A Randomized Phase 2 Study of MK-2206 in Comparison With Everolimus in Refractory Renal Cell Carcinoma (NCT01239342)
GDC-0980	Pan-isoform inhibitor of PI3-K and catalytic inhibitor of mTOR	A Phase II, Open Label, Randomized Study of GDC-0980 Versus Everolimus in Patients With Metastatic Renal Cell Carcinoma Who Have Progressed on or Following VEGF-Targeted Therapy (NCT01442090)
BEZ-235	Pan-isoform inhibitor of PI3-K and catalytic inhibitor of mTOR\	A Phase 1b/2 Study of BEZ235 in Patients With Advanced Renal Cell Carcinoma (RCC) (NCT01453595)