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REVIEW

Future directions of mammalian target of rapamycin (mTOR) inhibitor therapy in renal cell carcinoma

Sumanta Kumar Pal · Robert A. Figlin

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Abstract With an explosion of available treatments for metastatic renal cell carcinoma (mRCC) in recent years, it is important to recognize that approved targeted therapies fall broadly into only two mechanistic categories. The first category, vascular endothelial growth factor (VEGF)-directed therapies, includes sunitinib, pazopanib, sorafenib and bevacizumab. The second category includes inhibitors of the mammalian target of rapamycin (mTOR), namely everolimus and temsirolimus. A pivotal trial of everolimus supports use of the agent in patients with mRCC refractory to VEGF- tyrosine kinase inhibitors (TKI) therapy, while pivotal data for temsirolimus supports use in poor-prognosis patients as first-line therapy. Multiple reviews exist to delineate the laboratory and clinical development of mTOR inhibitors. This paper will outline the future applications of these therapies. It will explore ongoing trials evaluating combinations of mTOR inhibitors with other targeted therapies, along with sequencing strategies and biomarker discovery efforts. The application of mTOR inhibitors in unique populations is also described.

Keywords mTOR · Everolimus · Temsirolimus · Deferolimus · INTORACT · TORAVA · BeST · Biomarkers · Clinical trials

S. K. Pal (✉)
Division of Genitourinary Malignancies,
Department of Medical Oncology & Experimental Therapeutics,
City of Hope Comprehensive Cancer Center,
Los Angeles, CA, USA
e-mail: spal@coh.org

R. A. Figlin
Division of Hematology Oncology, Department of Medicine,
Cedars-Sinai Medical Center,
Los Angeles, CA, USA
e-mail: robert.figlin@cshs.org

R. A. Figlin
Academic Program Development,
Samuel Oschin Comprehensive Cancer Institute,
Los Angeles, CA, USA

R. A. Figlin
David Geffen School of Medicine at UCLA,
8700 Beverly Blvd., AC 1042-B, North Tower,
Los Angeles, CA 90048, USA

Introduction

Therapy for metastatic renal cell carcinoma (mRCC) has undergone a dramatic evolution in recent years. After the approval of interleukin-2 (IL-2) in 1992, an extended period ensued without any major therapeutic advances [1]. Although IL-2 yielded durable responses in a small subset of patients, the overwhelming majority obtained little benefit [2]. Nearly a decade after the approval of IL-2, Motzer et al. suggested that interferon-α (IFN-α) should be used as a comparator in further trials of novel therapies for mRCC [3]. Similar to IL-2, the data for IFN-α indicated only a modest clinical benefit, with meta-analysis data suggesting a median overall survival (OS) of 13 months.

Within the past 5 years, an explosion in drug development has occurred in the domain of mRCC, resulting in a dramatic improvement in outcomes. However, each of the six agents approved by the United States Food and Drug Administration (FDA) over this period of time can be divided into one of two mechanistic categories. In early 2007, phase III data for the vascular endothelial growth factor-tyrosine kinase inhibitors (VEGF-TKIs) sunitinib and sorafenib were published, preceded by their approvals [4–7]. The approvals of pazopanib (also a VEGF-TKI) and bevacizumab (a VEGF-directed monoclonal antibody)

ensued, following report of progression-free survival (PFS) benefit in pivotal trials evaluating these agents [8–10]. Notably, despite their characterization, VEGF-TKIs possess mechanisms that extend far beyond inhibition of the VEGF receptor (VEGFR) family of molecules, including inhibition of cell membrane receptors including platelet-derived growth factor receptor (PDGFR), KIT, fms-like tyrosine kinase receptor-3 (FLT3), and Raf.

In addition to VEGF-directed therapies, inhibition of the mammalian target of rapamycin (mTOR) has also been shown to represent a clinically viable anticancer strategy in mRCC. Two agents, everolimus and temsirolimus, are currently approved for the treatment of this disease [11, 12]. Everolimus was compared to placebo in a randomized, phase III RECORD-1 study including 410 patients with clear-cell mRCC that had progressed on sunitinib, sorafenib, or both [11]. The study met its primary endpoint, demonstrating an improvement in PFS of 2.1 months (4.0 versus 1.9 months, $P<0.0001$).In contrast, the phase III study of temsirolimus compared the single agent to temsirolimus with IFN-α or IFN-α alone in patients with previously untreated, poor-prognosis mRCC [12]. Therapy with single-agent temsirolimus led to an improvement in OS as compared to IFN-α (10.9 versus 7.3 months, $P<0.008$). Other mTOR inhibitors (i.e., deferolimus) are currently in clinical development, as are numerous combined inhibitors that dually target upstream moieties (i.e., BEZ235, BGT225) [13, 14].

There are multiple reviews that summarize the clinical development and current indications of temsirolimus and everolimus in the context of mRCC [15–20]. However, the current review will focus on novel applications of mTOR inhibitors. Ongoing efforts exploring combination therapy, sequencing strategies, and biomarkers are described (see Tables 1 and 2). Furthermore, current strategies to investigate the utility of mTOR inhibitors in specific populations are discussed.

Combination therapy

At present, numerous combinations of everolimus and temsirolimus with other cytotoxic agents are being explored. Data is available from only a fraction of these studies to date. The combination of sunitinib and temsirolimus was explored in a phase I clinical trial; however, two dose-limiting toxicities (DLTs) were observed among three patients within the first cohort receiving sunitinib at 25 mg daily and temsirolimus at 15 mg weekly [21]. As a consequence, this study was terminated. Sorafenib and temsirolimus in combination have been explored in several malignancies outside of RCC, including glioblastoma, melanoma, and hepatocellular carcinoma [22–24]. Phase I data for the combination suggested significant palmar-plantar erythrodysesthesias using full doses of both, although there was no pharmacokinetic interaction [25]. The randomized, phase II BeST study explores four permutations of bevacizumab, sorafenib and temsirolimus (including sorafenib with temsirolimus) in patients with mRCC [26]. The study is anticipated to enroll a total of 360 patients with a primary completion date in May of 2012.

The combination of bevacizumab and temsirolimus has recently received a great deal of attention. The phase I component of a phase I/II trial utilizing this regimen identified a recommended dose of temsirolimus 25 mg weekly and bevacizumab 10 mg/kg every 2 weeks [27]. DLTs incurred with the combination at these doses included hypertriglyceridemia and mucositis. Early data from the phase II component of this study were somewhat encouraging, with 4 patients (16%) experiencing a partial response (PR) and 18 patients (72%) with stable disease (SD) [28]. Enthusiasm for this regimen has been tempered by the recent results of the TORAVA study. In this trial, 171 patients were randomized in a 2:1:1 fashion to bevacizumab/temsirolimus, sunitinib or bevacizumab/IFN-α. Response rates were 25%, 24% and 34%, respectively. Non-progression rate at 48 weeks (the primary endpoint of the trial) was 43.2%, 47.6%, and 65.9%, respectively. The experimental arm (bevacizumab/temsirolimus) was accompanied by significant rates of toxicity, with upwards of 40% of patients discontinuing therapy for this reason. A specific focus on grade ≥3 events suggested a relatively high rate of colonic fistulas and hemorrhage. Moving forward, two large trials will further prospectively assess the combination with bevacizumab—the aforementioned BeST study an the phase III INTORACT trial [29, 30]. INTORACT will randomize 800 patients to either bevacizumab/temsirolimus or bevacizumab/IFN-α [29]. While the results of INTORACT are eagerly anticipated, the experience garnered from TORAVA underscores the importance of examining regimens in the phase II setting prior to embarking on larger phase III efforts.

Most recently, data has emerged exploring the combination of temsirolimus with the novel VEGF-TKI tivozanib (AV-951).Tivozanib has affinity for VEGFR-1, -2, and -3, and has been assessed in a randomized discontinuation study enrolling 272 patients with all types of mRCC histology [31]. Approximately 73% of the patients in this study had received prior nephrectomy, and 46% had received prior systemic therapy. Even with this degree of prior treatment, treatment with tivozanib elicited an overall response rate(RR) of 25.4% and a median progression-free survival(PFS) of 11.8 months. PFS was similar among patients who were treatment naïve and among patients who had received prior therapy. The combination of tivozanib and temsirolimus was explored in a phase I study including patients with mRCC and a clear-cell component, with no

Table 1 Planned and ongoing trials of everolimus in renal cell carcinoma

NCI Identifier	Title
Combinations	
NCT01037257 [75]	A safety study of LBH589 (Panobinostat) and RAD001 (Everolimus) to stabilize kidney cancer
NCT01198158 [76]	Everolimus with or without bevacizumab in treating patients with advanced kidney cancer that progressed after first-line therapy
NCT01239342 [77]	MK2206 or everolimus in treating patients with refractory kidney cancer
NCT01218555 [78]	Study of everolimus (RAD001) in combination with lenalidomide in patients with advanced solid malignancies enriched for renal cell carcinoma
NCT01115803 [79]	A study of LY2584702 with erlotinib or everolimus in patients with solid tumors
NCT00303732 [80]	Vatalanib and everolimus in treating patients with advanced solid tumors
NCT00651482 [81]	Treatment of refractory metastatic renal cell carcinoma with bevacizumab and RADOO1
NCT00422344 [82]	A study of RAD001 and sunitinib in metastatic renal cell carcinoma
NCT01034631 [83]	BNC105P in combination with everolimus/following everolimus for progressive Metastatic clear cell renal cell carcinoma
NCT00384969 [84]	Sorafenib and RAD001 renal cell carcinoma
NCT00719264 [85]	Safety and efficacy of bevacizumab plus RAD001 versus interferon alfa-2a and bevacizumab in adult patients with kidney cancer (L2201)
NCT00331409 [86]	Everolimus and imatinib mesylate in treating patients with metastatic or unresectable kidney cancer
NCT00655655 [87]	Everolimus and vatalanib in treating patients with advanced solid tumors
NCT00392821 [88]	Dosing and effectiveness study of sorafenib and RAD001 in the treatment of patients with advanced kidney cancer
NCT00323739 [89]	Bevacizumab (Avastin) and RAD001(Everolimus)in the treatment of advanced clear cell renal carcinoma
NCT00985374 [90]	A multiple ascending dose study of the mTOR inhibitor (RAD001) in combination with R1507 in patients with advanced solid tumors
NCT01184326 [91]	Pazopanib and everolimus in patients with advanced solid tumors and previously treated kidney cancer
NCT00788060 [92]	A phase Ib study of Rad001 and sutent to treat renal cell carcinoma (Rad/Sutent)
NCT01136733 [93]	A study of E7080 alone, and in combination with everolimus in subjects with unresectable advanced or metastatic renal cell carcinoma following one prior Vascular Endothelial Growth Factor (VEGF)-targeted treatment
NCT00448149 [94]	Phase I/II trial of RAD001 plus nexavar in patients with kidney cancer
Sequencing	
NCT00903175 [95]	Efficacy and safety comparison of RAD001 versus sunitinib in the first-line and second-line treatment of patients with metastatic renal cell carcinoma
NCT01217931 [38]	Sequential two-agent assessment in renal cell carcinoma therapy
Neo-adjuvant/adjuvant therapy	
NCT01107509 [47]	Pilot study of neo-adjuvant everolimus to treat advanced renal cell carcinoma—analysis of biomarkers
NCT01120249 [43]	Everolimus in treating patients with kidney cancer who have undergone surgery
NCT00831480 [96]	Everolimus(RAD001) for advanced Renal Cell Carcinoma(RCC) before kidney removal
Biomarker discovery/imaging	
NCT01028638 [74]	VEGF imaging before and during everolimus treatment for renal cell carcinoma
NCT00529802 [66]	Exploratory study evaluating fluorodeoxyglucose—position emission tomography as a predictive marker for therapy with RAD001 in metastatic renal cell cancer
NCT00827359 [62]	Biomarker trial of everolimus in patients with advanced renal cell carcinoma
Unique populations	
NCT01152801 [57]	Safety of RAD001 in Chinese patients with metastatic renal cell cancer
NCT01206764 [56]	A trial of everolimis in patients with advanced renal cell carcinoma (EVERMORE)
Non-clear cell	
NCT00830895 [52]	RAD001 for non-clear cell Renal Cell Carcinoma (RCC)
NCT00688753 [53]	RAPTOR: RAD001 as monotherapy in the treatment of advanced papillary renal cell tumors program in Europe (RAPTOR/LFR08)
NCT01185366 [97]	Everolimus versus sunitinib in non-clear cell renal cell carcinoma
NCT01108445 [51]	Phase II study of afinitor vs. sutent in patients with metastatic non-clear cell renal cell carcinoma (ASPEN)

Table 2 Planned and ongoing trials of temsirolimus in renal cell carcinoma

NCI Identifier	Title
Combinations	
NCT00700258 [98]	Registry for temsirolimus and sunitinib treated patients with metastatic Renal Cell Carcinoma (mRCC), Mantle Cell Lymphoma (MCL), and Gastro-Intestinal Stroma Tumor (GIST) [STAR-TOR]
NCT00112840 [99]	CCI-779 and bevacizumab in treating patients with metastatic or unresectable kidney cancer
NCT00782275 [100]	Avastin and temsirolimus following tyrosine kinase inhibitor failure in patients with advanced renal cell carcinoma
NCT00563147 [101]	A phase 1b, open-label, dose-finding study to evaluate the safety of tivozanib (AV-951) in combination with temsirolimus in subjects with metastatic renal cell carcinoma
NCT00417677 [102]	A study combining treatment with temsirolimus and sunitinib for subjects with advanced renal cell carcinoma
NCT00631371 [29]	Study comparing bevacizumab+temsirolimus vs. bevacizumab+interferon-alfa in advanced renal cell carcinoma subjects (INTORACT)
NCT00065468 [103]	Study evaluating interferon and CCI-779 in advanced Renal Cell Carcinoma (ARCC)
NCT00378703 [104]	Bevacizumab, sorafenib, and temsirolimus in treating patients with metastatic kidney cancer
NCT00619268 [105]	Combination of temsirolimus and bevacizumab in patient with metastatic renal cell carcinoma (TORAVA)
NCT01079286 [106]	Study of nelfinavir and temsirolimus in patients with advanced cancers (I-NET)
NCT00112476 [107]	Temsirolimus and bryostatin 1 in treating patients with unresectable or metastatic solid tumors
NCT00600496 [108]	A phase I, open-label, multi-center study to assess the safety, tolerability and pharmacokinetics of AZD6244 (ARRY-142886)
NCT01198184 [109]	RO4929097 and temsirolimus in treating patients with advanced solid tumors
NCT01122615 [110]	Sunitinib plus temsirolimus in patients with Renal Cell Cancer (RCC)
NCT01155258 [111]	Temsirolimus and vinorelbine ditartrate in treating patients with unresectable or metastatic solid tumors
NCT00659568 [112]	Metformin and temsirolimus in treating patients with metastatic or unresectable solid tumor or lymphoma
Sequencing	
NCT00474786 [39]	Temsirolimus versus sorafenib as second-line therapy in patients with advanced RCC who have failed first-line sunitinib
Biomarker discovery/imaging	
NCT01246817 [67]	Temsirolimus-RCC-imaging
NCT01224288 [73]	Renal Cell Carcinoma (RCC) scramble
NCT00538772 [113]	An exploratory correlative study of biomarkers in patients with metastatic renal cell carcinoma who have progressed after sunitinib therapy[a]
Unique populations	
NCT00494091 [58]	Study evaluating the safety, efficacy & pharmacokinetics of temsirolimus(CCI-779) in subjects with advanced renal cell carcinoma
Non-clear cell	
NCT00979966 [50]	Study in non-clear cell renal carcinoma (Ncc-RCC) temsirolimus versus sunitinib

[a] Study withdrawn prior to patient enrollment

more than one prior VEGF-directed therapy and no prior mTOR inhibitor therapy [32]. Tivozanib was administered once daily for 3 weeks with a 1 week break thereafter, and temsirolimus was administered weekly. The maximally tolerated dose (MTD) for tivozanib and temsirolimus were 1.5 mg daily and 25 mg weekly, respectively. Of 14 evaluable patients, 2 had confirmed PR and 8 had SD in excess of 10 weeks. Encouraging clinical activity with this combination will likely prompt further study.

As with temsirolimus, everolimus has been paired with a number of emerging targeted therapies. The combination of sorafenib with temsirolimus was explored in a cohort of 18 patients. The combination appeared to be relatively well tolerated, with the MTD comprised of standard doses of both drugs (i.e., sorafenib 400 mg twice daily and everolimus 10 mg daily) [33]. Several concerning toxicities were highlighted, however: DLTs in this trial included pneumonitis, pulmonary embolism, and thrombocytopenia. The combination of sunitinib and everolimus has also been explored in a phase I trial enrolling 20 patients with mRCC (notably, 7 patients with non-clear cell histology were included) [34]. The recommended phase II dose was 20 mg of everolimus weekly in combination with 37.5 mg of sunitinib daily. A total of 5 patients were noted to have PR, and among these were 2 patients with papillary RCC and 1 patient with chromophobe RCC. Moving forward, it will be

interesting to characterize the activity of this regimen in larger cohorts of non-clear cell patients.

Like bevacizumab with temsirolimus, the combination of bevacizumab with everolimus appears to be well tolerated. A phase I study of the combination identified a recommended phase II dose of bevacizumab at 10 mg/kg every 2 weeks with everolimus at 10 mg daily [35]. A follow-up phase II study employing this regimen included 80 patients with mRCC. Treatment-naïve patients in this cohort had a median PFS of 9.1 months, as compared to 7.1 months in pre-treated patients. The overall response rate (ORR) in treatment-naïve patients was 30%. The rates of grade 3/4 proteinuria were considerable (25%), but the rates of toxicity were otherwise reasonable [36]. The recently completed RECORD-2 study will further compare bevacizumab/everolimus to bevacizumab/IFN-α in 360 patients with mRCC [37].

Outside of VEGF-directed therapies, there are a plethora of early clinical trials exploring combinations of everolimus and temsirolimus with novel targeted therapies, cytotoxic agents, and immunotherapy. Combination studies including patients with mRCC and incorporating everolimus and temsirolimus are depicted in Figs. 1 and 2. Limited data are available from these efforts at this point.

Optimizing the sequence of therapy

There are limited examples of trials incorporating mTOR inhibitors that employ a direct, sequential design (i.e., A→B versus B→A). One such study is RECORD-3, a randomized, phase II effort comparing sunitinib to everolimus in patients with treatment-naïve mRCC. At the time of progression on either first-line therapy, patients are crossed over to the other treatment arm. The primary outcome measure in the study is PFS after first-line therapy, with secondary endpoints including PFS after second-line therapy, OS, and objective response rates during each line of therapy. Employing a non-inferiority design, the study will accrue a total of 390 patients with an anticipated completion date in April of 2013. Results of this study have the potential to alter the paradigm established by the RECORD-1 trial [11]. If the sequence of everolimus followed by sunitinib is found to be non-inferior, up-front therapy with an mTOR inhibitor could be considered.

A second study that may identify an optimal sequence of targeted therapy is being coordinated by the MD Anderson Cancer Center [38]. The Sequential Two-agent Assessment in Renal Cell Carcinoma Therapy (START) trial will enroll a total of 240 patients and will randomize the patients to various permutations of pazopanib, bevacizumab and everolimus. The primary endpoint of the study is time to overall treatment failure, which is measured from the randomization date to the date of second disease progression.

The data for everolimus derived from RECORD-1 support therapy with the agent after either sunitinib or sorafenib, or both [11]. As such, there is a lack of clarity regarding whether mTOR inhibition is a superior strategy for second-line therapy. Although not a "sequencing" trial in its truest form, a randomized comparison between temsirolimus and sorafenib may aid in resolving this clinical dilemma [39]. The study assesses patients who have specifically failed first-line therapy with sunitinib, and is powered to compare the PFS associated with each agent. The study will enroll a total of 480 patients, with an estimated completion date in May of 2011.

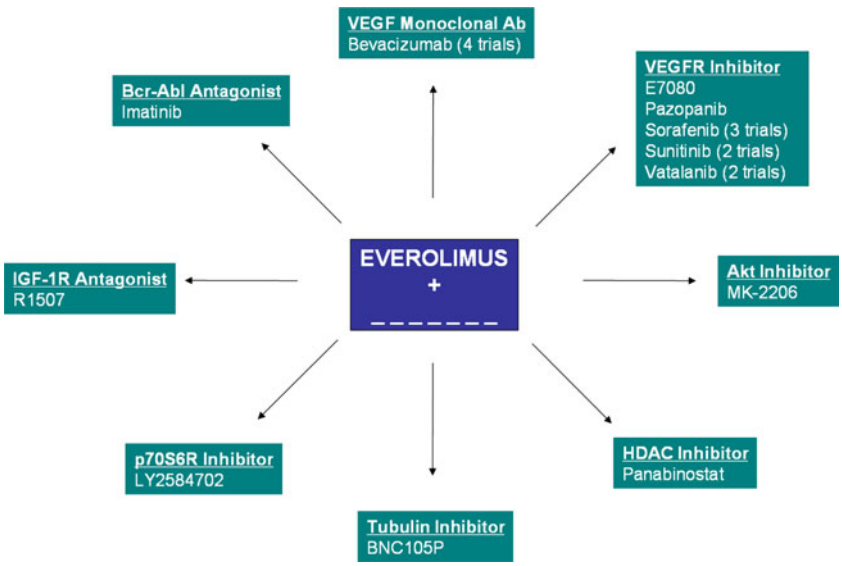

Fig. 1 Planned and ongoing combination therapy trials incorporating everolimus

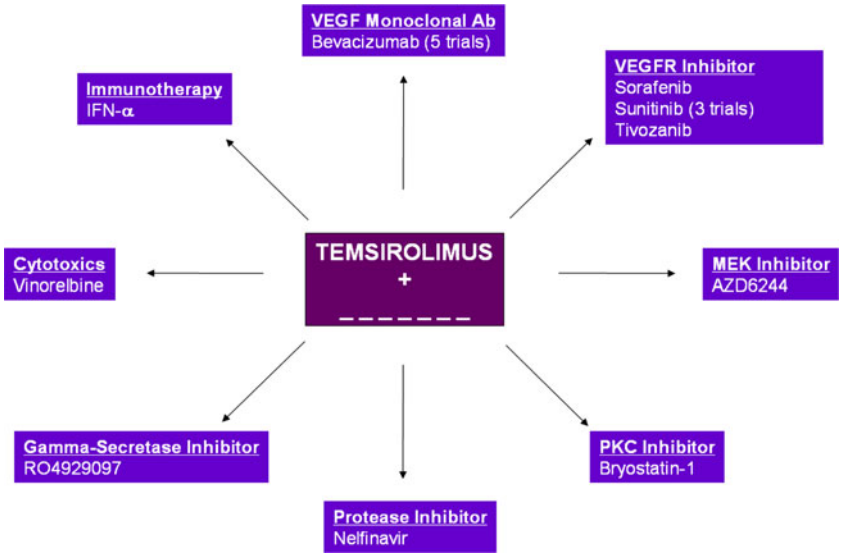

Fig. 2 Planned and ongoing combination therapy trials incorporating temsirolimus

Neo-adjuvant and adjuvant therapy

At present, there is no evidence to support use of targeted agents as adjuvant therapy for patients with localized RCC following nephrectomy. However, several trials are underway to explore this indication. The Eastern Cooperative Oncology Group (ECOG) has recently completed a trial (ECOG 2805) comparing 1 year of adjuvant sunitinib, sorafenib and placebo in 1,923 patients with localized RCC [40]. The study is powered to assess disease-free survival (DFS) in the three treatment groups. In contrast to ECOG 2805, the Sunitinib-Treatment of Renal Adjuvant Cancer (S-TRAC) study will randomize 600 patients to either sunitinib or placebo, while the SORCE trial will randomize 1,656 patients to receive either sorafenib or placebo [41, 42]. While trials of VEGF-TKIs as adjuvant therapy are abundant, there are more limited efforts exploring mTOR inhibitors in this context. The EVEREST trial, led by the Southwest Oncology Group (SWOG), will randomize 1,218 patients to either everolimus or placebo [43]. Eligibility requirements include RCC histology (excluding collecting duct and medullary carcinoma), negative surgical margins, and intermediate high-risk or very high-risk disease. Patients will receive a total of nine six-week cycles of therapy, with a primary end-point of recurrence-free survival (RFS).Correlative studies accompanying EVEREST will assess nephrectomy specimens for moieties along the AKT/mTOR signaling cascade, and will further assess steady-state trough concentrations of everolimus.

Neo-adjuvant trials offer a prime opportunity to ascertain the biologic effects of targeted therapies. Akin to the adjuvant setting, multiple studies have been established to explore neo-adjuvant therapy with VEGF-TKIs [44–46]. However, relatively few neo-adjuvant trials of mTOR inhibitors have been pursued to date. A neoadjuvant study of everolimus will enroll 20 patients with localized clear cell RCC (T2–4, or any stage with N1–2 disease) or metastatic clear-cell RCC [47]. Both blood and tissue biomarkers will be assessed in this study.

Non-clear cell RCC

Retrospective analyses suggest limited activity of VEGF-TKIs in non-clear cell renal cell carcinoma. As one example, Choueiri et al. assessed 53 patients with metastatic papillary or renal cell carcinoma treated in either France or the United States with either sunitinib or sorafenib [48]. The ORR for the entire cohort was only 10%; median OS was 19.6 months. Of 12 patients with chromophobe mRCC, 3 patients (25%) achieved PR. Only 2 (4.8%) of 41 patients with papillary mRCC achieved a response—notably, both had been treated with sunitinib. Plimack et al. reported a prospective experience assessing sunitinib in 23 patients with papillary mRCC [49]. The primary endpoint in this study was RR and PFS. Median PFS was a sobering 1.6 months (95%CI: 1.3–12 months), and no responses were observed. SD was observed as a best response in 8 patients, and the median OS in the cohort was 10.8 months.

The pivotal trial of temsirolimus (comparing temsirolimus with or without IFN-α to IFN-α alone) was unique in inclusion of non-clear cell patients. Of the 626 patients enrolled into the study, 124 (20%) had a non-clear cell histology [12]. A total of 73 non-clear cell mRCC patients received either temsirolimus or IFN-α, and analysis of this subset with respect to OS favored temsirolimus therapy. These compelling data have prompted further exploration of mTOR inhibitors in patients with papillary and chromophobe histologies. A prospective, randomized phase II study conducted by the Central European Society for Anticancer

Drug Research will treat 108 patients with non-clear cell mRCC with either sunitinib or temsirolimus at standard doses [50]. The primary endpoint of the study is time to progression.

There is also considerable interest in exploring the role of everolimus in the same setting. The Phase II ASPEN study will randomize patients with non-clear cell RCC to receive either everolimus or sunitinib [51]. The study will also accrue a total of 108 patients, with a primary endpoint of PFS. Unique secondary outcome measures in this study include a comparison of antitumor activity to a historical cohort comprised of similar patients treated with IFN-α. A straightforward single-arm, phase II study of everolimus in non-clear cell mRCC is ongoing in Korea, and is anticipated to enroll 48 patients [52]. Specific to patients with papillary mRCC, the RAPTOR study will explore everolimus in a single-arm, phase II design [53]. The primary endpoint of the study is PFS at 6 months, with an anticipated enrollment of 60 patients.

Specific populations

Available datasets for a range of targeted therapies have suggested specific risk: benefit profiles that vary with geographic distribution and/or race. For instance, in a pivotal trial in non-small cell lung cancer (NSCLC), it was suggested that Asian origin (among limited other clinico-pathologic criteria) was associated with improved OS with erlotinib therapy [54]. As another prominent example, hypersensitivity reactions associated with cetuximab therapy have been noted to occur in specific territories within the United States [55]. Observations such as these have prompted exploration of targeted therapies for renal cell carcinoma in underrepresented populations. Two trials of everolimus fall into this category. The EVERMORE trial is an open-label phase II study that will assess patients with mRCC (any histology) who may have received cytokine therapy, but have not previously received VEGF-directed therapies or mTOR inhibitors [56]. The study will accrue a total of 110 patients from centers located in Africa, the Middle East, Southeast Asia and Russia, and explores a primary endpoint of PFS. A separate phase Ib trial of everolimus will be conducted in China [57]. The study will enroll patients who have progressed on VEGF-TKI therapy; prior cytokine therapy is also permitted. A total of 60 patients are anticipated to accrue to this effort. With respect to temsirolimus, one study is exploring two dose-levels of the agent in Korean, Japanese, or Chinese patients with mRCC, irrespective of histology or prior therapy [58]. A small cohort of Japanese patients with mRCC (n=6) will be treated with temsirolimus at a weekly dose of 20 mg intravenous. The remainder of the cohort (to total 80 patients) will receive temsirolimus at standard doses (i.e., 25 mg intravenous weekly).

Biomarker discovery

To date, the majority of efforts to characterize biomarkers predicting clinical benefit from mTOR inhibitors are retrospective. Few of these studies have yielded salient biomarkers. One notable exception emerges from the pivotal trial of temsirolimus. In this study, it was noted that an elevated LDH was associated with an improved OS with temsirolimus therapy (P<0.002) as compared to IFN-α [59]. In contrast, patients with a normal LDH did not obtain a survival benefit relative to patients treated with IFN-α. Other efforts to correlate biomarkers to clinical outcome with mTOR inhibitor therapy have been somewhat disappointing. For example, baseline levels PTEN and HIF-1α were also assessed in the phase III evaluation of temsirolimus [60]. However, neither demonstrated correlation with response; PFS and OS were improved with temsirolimus therapy irrespective of the levels of these markers.

Given the limitations of biomarker development using retrospective datasets, the research community has often cited the need for prospective efforts powered to assess novel biomarkers [61]. Unfortunately, few examples of biomarker-driven trial designs (as they pertain to mTOR inhibitor therapy) exist. A novel phase II biomarker-driven study of everolimus (coordinated by the Beth Israel Deaconess Medical Center) is planned [62]. This study would enroll 40 patients with mRCC, and requires the presence of metastatic lesions that are amenable to biopsy. The primary objective of the study is to prospectively validate phosphorylated-Akt and -S6 as biomarkers of everolimus response. Secondary objectives in this study include not only clinical response, but assessment of a panel of novel biomarkers including phosphorylated PRAS40, phosphorylated TSC, and elF4E. It is critical that the scientific community lend support to translational efforts such as this, which will certainly amass valuable information regarding putative biomarkers of mTOR inhibitor efficacy.

Outside of characterizing molecular mediators, novel imaging techniques may provide unique insights into subsets of patients with mRCC that derive benefit from mTOR inhibitors. Varying reports exist regarding the potential predictive capabilities of positron emission tomography (PET) in patients treated with mTOR inhibitors. In vivo preclinical studies suggest that fluorodeoxyglucose (FDG) uptake can be used to define the optimal biologic dose of everolimus therapy [63]. Supporting this, a study of eight patients with NSCLC treated with everolimus suggested marked reductions of ^{18}F-FDG uptake within just days of

initiating therapy, suggesting that this may be an early effect of everolimus treatment [64]. These encouraging reports are tempered by others; for instance, an assessment of 34 cancer patients treated with rapamycin analogues suggested that changes in ^{18}F-FDG PET may be indicative of changes in Akt activation, but was not necessarily predictive of therapeutic response [65].

In the setting of mRCC, a recently completed study at the University of Chicago assessed a cohort of 60 patients receiving everolimus with ^{18}F-FDG-PET [66]. Enrolled patients were refractory to sunitinib and/or sorafenib. The principal aim of the study was to determine if high uptake on PET at an 8-week interval was correlated with the extent of tumor shrinkage. Results from this study are eagerly awaited. A second study centered in the Netherlands will assess 51 mRCC patients receiving temsirolimus with standard ^{18}F-FDG-PET, as well as ^{18}F-fluoro-L-thymidine (^{18}F-FLT)-PET [67]. Patients must have progressed on at least one prior antiangiogenic agent. ^{18}F-FLT-PET has been developed as a modality to image the extent of tumor cell proliferation, and therefore may be highly useful in interpreting the activity of largely cytostatic agents such as temsirolimus [68–72].

Several other novel imaging modalities are under evaluation for mRCC patients receiving mTOR inhibitor therapy. The RCC Scramble study, a companion to the aforementioned START trial, will assess patients receiving sequential targeted therapies (including everolimus) with dynamic contrast-enhanced computed tomography (DCE-CT) [38, 73]. DCE-CT provides an estimate of blood flow to tumor tissue; as a consequence, the modality may offer greater biological insight into the efficacy of mTOR inhibitor therapy. A second study centered in the Netherlands will assess VEGF production in 14 patients with mRCC receiving everolimus using ^{89}Zr-labelled bevacizumab [74]. The primary outcome measure in the study is correlation between ^{89}Zr- bevacizumab uptake on baseline scan and on-treatment scans performed at 2 and 6 weeks. Novel imaging studies such as these may ultimately offer a substitute for algorithms such as RECIST, which often cannot account for antitumor activity reflected in tumor necrosis and cavitation.

Conclusions

The multitude of described and ongoing trials (Tables 1 and 2) [75–113] suggests that the clinical development strategy for everolimus and temsirolimus in mRCC extend far beyond their current indications. While these efforts are to be applauded, the research community will ultimately be challenged to prioritize them in the coming years. For instance, how does the necessity of large combination therapy trials (i.e., RECORD-2 and INTORACT) compare with the necessity to evaluate novel mTOR inhibitors, such as deferolimus? Do sequencing strategies or biomarker discovery serve as the ideal manner in which to resolve current areas of equipoise in therapeutic assignment? Will large, comparative trials be necessary to juxtapose the effect of combined inhibitors (i.e., BEZ235) against currently available agents? While the number of clinical dilemmas in RCC therapy is limitless, the availability of appropriate study patients is not. In the future, the research community will need to unite to develop a cohesive strategy to optimize use of available agents that move the efforts in renal cell carcinoma forward and identify the optimal strategies on behalf of our patients.

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