Sequential Treatment Strategies and Combination Therapy Regimens in Metastatic Renal Cell Carcinoma

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Abstract: Molecularly-targeted therapies have revolutionized the treatment of metastatic renal cell carcinoma (mRCC), but unmet needs remain. Efficacy of targeted agents is transient, and questions regarding optimal sequencing of therapies and benefits versus risks of combination therapy remain largely unanswered. In this article, an overview of ongoing/recently completed clinical trials evaluating sequential treatment strategies and combination therapy regimens is presented, along with a brief discussion of predictive biomarkers and prognostic factors. Several ongoing/recently completed clinical studies have been designed to help address 2 major questions currently facing physicians treating patients with mRCC: 1) What is the optimal sequence of targeted agents? and 2) Does combination therapy with targeted agents benefit patients with mRCC? Results of these trials may help establish the degree to which cross-resistance between agents occurs and which agents, when used consecutively, are associated with the most favorable outcomes. Clinical trial data maturing in the next 1–2 years should provide insight into the most effective treatment sequences and the benefits versus risks of combination therapies. Whether results of these studies will lead to a paradigm shift in treatment recommendations for patients with mRCC remains to be determined.

Introduction

In the United States, the incidence of renal cell carcinoma (RCC) continues to grow, and the prognosis for metastatic RCC (mRCC) remains poor. In 2010, an estimated 58,240 new cases of kidney and renal pelvis cancer were reported and 13,040 deaths occurred.[1] Metastatic progression significantly increases the likelihood of mortality; the 5-year survival rate for patients with metastatic renal disease at the time of diagnosis is 11%.[2] Notably, even among patients with confined disease at the time of nephrectomy, 10–24% experience subsequent recurrence.[3-5] Thus, effective systemic treatment options for mRCC are needed.

Molecularly-targeted therapies currently represent the principal treatment approach for patients with mRCC. Seven agents have become available since 2005, broadly falling into 2 distinct mechanistic categories: vascular endothelial growth factor (VEGF)-based therapies and mammalian target of rapamycin (mTOR) inhibitors. The former category consists of the VEGF receptor-tyrosine kinase inhibitors (VEGFr-TKIs) sorafenib (Nexavar, Bayer/Onyx), sunitinib (Sutent, Pfizer), pazopanib (Votrient, GlaxoSmithKline), and axitinib (Inlyta, Pfizer); and the anti-VEGF monoclonal antibody bevacizumab (Avastin, Genentech; administered with interferon alfa [IFN-α]). The mTOR inhibitors include temsirolimus (Torisel, Pfizer) and everolimus (Afinitor, Novartis). Aside from axitinib (which was approved by the US Food and Drug Administration [FDA] in January 2012 for use in patients with mRCC after failure of 1 previous systemic therapy),[6] the remaining 6 targeted agents are approved by both the FDA and the European Medicines Agency for the treatment of mRCC. Approvals were based on results of pivotal phase III clinical trials. As summarized in Table 1, targeted agents improved tumor responses and prolonged progression-free survival (PFS).[7-18] Some studies also demonstrated prolongation of overall survival (OS),[7,8,10-12,14] although this parameter was likely confounded because patients originally assigned to placebo were allowed to cross over to active treatment.[8,10,14] In combination studies, IFN-α with bevacizumab was more effective than without[10,11]; however, temsirolimus added to IFN-α was less effective than temsirolimus alone.[12] In both studies, adverse events (AEs) occurred more frequently with combination therapy than with monotherapy.[10,12]

The current mRCC treatment paradigm is typically composed of sequential monotherapy with targeted agents. Guidelines continue to evolve regarding which agent to use as first-line therapy in treatment-naïve patients and as second-line therapy after relapse. Multiple clinical practice guidelines for mRCC have been released in the United States and Europe, including those issued by the National Comprehensive Cancer Network (NCCN),[19] the European Society for Medical Oncology (ESMO),[20] the European Organization for Research and Treatment of Cancer (EORTC),[21] and the European Association of Urology (EAU).[22] Per 2012 NCCN guidelines, for treatment-naïve patients, first-line options supported by the highest level of clinical evidence (category 1) include sunitinib, bevacizumab plus IFN-α, and pazopanib (risk classifications not specified). Temsirolimus is recommended specifically for poor-prognosis patients (high risk).[19] Thus, for most patients with mRCC, VEGF-based therapies have become standard-of-care first-line treatment. However, benefits are transient. Durable response

is rarely achieved, and most patients eventually develop progressive disease. Resistance to VEGFr-TKIs develops at a median of 6–11 months.[15,16] Second-line recommendations with highest clinical evidence (category 1) in the NCCN clinical guidelines include axitinib following 1 previous systemic therapy; sorafenib, sunitinib, and pazopanib following previous cytokine therapy; and everolimus following previous VEGFr-TKI therapy.[19]

Recommendations based on lower-level clinical evidence (eg, nonrandomized controlled trials) suggest sorafenib, sunitinib, pazopanib, bevacizumab plus IFN-α, or temsirolimus as second-line treatment following relapse on VEGFr-TKIs, and bevacizumab plus IFN-α or temsirolimus after failure on cytokine therapy.[19] Thus, current guidelines reflect a broad range of treatment/sequencing choices for first- and second-line therapy, leaving clinicians with several options when making treatment decisions.

Despite these substantial advances, gaps remain in our current understanding regarding optimal harnessing of the therapeutic potential of these agents. Certain treatment choices are not yet reflected in current guidelines, including expectant management in very-good-risk patients, first-line use of mTOR inhibitors in good- or intermediate-risk patients, second-line treatment following progression on an mTOR inhibitor, and recommendations for third-line therapy. In this review, we focus on key ongoing clinical trials expected to mature in the next 1–2 years and recently completed trials that may affect the mRCC treatment paradigm. Placing the design and potential outcomes of these ongoing studies into perspective may provide insight into 2 major questions facing physicians treating patients with mRCC: 1) What is the optimal sequence of targeted agents? and 2) Does combination therapy with targeted agents benefit patients with mRCC?

Many Treatment Options, Few Mechanistic Approaches

Clear cell RCC pathogenesis centers around inactivation of the von Hippel–Lindau (VHL) tumor suppressor gene, ultimately leading to aberrant VEGF signaling.[23-25] The VHL gene encodes for VHL protein, which is involved in degradation of hypoxia-inducible factor-α (HIF-α). Inactivation of VHL leads to uninhibited activity of HIF-α and subsequent upregulated transcription of various hypoxia-inducible genes, including VEGF and platelet-derived growth factor.[24] Binding of the VEGF ligand to its tyrosine kinase receptors triggers downstream signaling cascades that result in increased vascular permeability and endothelial cell survival, migration, and proliferation.[23-25] HIF-α levels are increased further through signaling by mTOR.[23]

Table 1. Summary of Phase III Pivotal Studies Upon Which Approval of Targeted Agents for mRCC Was Based

Targeted Agent/ Line of Treatment	Study Design	Median PFS (Overall Population)
Sunitinib vs IFN-α[7,15]	• Phase III, randomized; treatment-naïve patients • Sunitinib, n=375 • IFN-α, n=375	• Sunitinib: 11 months • IFN-α: 5 months HR, 0.539; 95% CI, 0.451–0.643; *P*<.001
Sorafenib vs placebo (TARGET)[8,16]	• Phase III, double-blind, randomized, placebo-controlled; relapsed on 1 systemic (primarily cytokine-based) treatment • Sorafenib, n=451 • Placebo, n=452	• Sorafenib: 5.5 months • Placebo: 2.8 months HR, 0.44; 95% CI, 0.35–0.55; *P*<.000001
Axitinib vs sorafenib (AXIS)[17]	• Phase III, randomized, open-label; relapsed on 1 prior first-line treatment with sunitinib-, BEV-, temsirolimus-, or cytokine-based therapy • Axitinib, n=361 • Sorafenib, n=362	• Axitinib: 6.7 months • Sorafenib: 4.7 months HR, 0.665; 95% CI, 0.544–0.812; *P*<.0001
Pazopanib vs placebo[9]	• Phase III, randomized, double-blind, placebo-controlled; treatment-naïve and cytokine-pretreated (IL-2 or IFN-α) • Pazopanib, n=290 • Placebo, n=145	• Pazopanib: 9.2 months • Placebo: 4.2 months HR, 0.46; 95% CI, 0.34–0.62; *P*<.0001
BEV + IFN-α vs placebo + IFN-α (AVOREN)[10,18]	• Phase III, randomized, double-blind; no prior systemic treatment for mRCC • BEV + IFN-α , n=327 • Placebo + IFN-α, n=322	• BEV + IFN-α: 10.2 months • Placebo + IFN-α: 5.4 months HR, 0.63; 95% CI, 0.52–0.75; *P*=.0001
BEV + IFN-α vs IFN-α (CALGB 90206)[11]	• Phase III, open-label; no prior systemic treatment for mRCC • BEV + IFN-α, n=369 • IFN monotherapy, n=363	• BEV + IFN-α: 8.4 months • IFN monotherapy: 4.9 months *P*<.0001
Temsirolimus, IFN-α, or both[12]	• Phase III, randomized; no prior systemic treatment for mRCC; ≥3 of 6 predictors of short survival • IFN-α, n=207 • Temsirolimus, n=209 • IFN-α + temsirolimus, n=210	• Temsirolimus: 3.8 months • IFN-α alone: 1.9 months • IFN-α + temsirolimus 3.7 months
Everolimus vs placebo (RECORD-1)[13,14]	• Phase III, randomized, double-blind, placebo-controlled • Refractory to sunitinib and/or sorafenib • Everolimus, n=272 • Placebo, n=138	• Everolimus: 4.9 months • Placebo: 1.9 months HR, 0.33; 95% CI, 0.25–0.43; *P*<.001

BEV=bevacizumab; CI=confidence interval; HR=hazard ratio; IFN-α=interferon alfa; IL-2=interleukin-2; mRCC=metastatic renal cell carcinoma; PFS=progression-free survival.

Current treatments for mRCC exert antitumor effects through 2 key mechanistic approaches, targeting distinct pathways in the VHL/HIF-α signaling cascade: VEGF signaling and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mTOR signaling. Currently approved VEGF-targeted therapies inhibit VEGF signaling through reduction in circulating VEGF ligand levels (eg, bevacizumab) or inhibition of select VEGF receptors (eg, sorafenib, sunitinib, pazopanib, axitinib), thereby blocking tumor angiogenesis.[26] mTOR, a serine/threonine protein kinase, plays a central role in cell growth/proliferation, angiogenesis, and cell metabolism by transducing various signals mediated through the PI3K/Akt pathway.[27-29] mTOR exists in 2 multiprotein complexes: mTORC1 and mTORC2. mTORC1 is involved in protein translation and metabolism-related functions, whereas mTORC2 is involved in regulation of kinase Akt activity.[30-32] Everolimus and temsirolimus exert cytotoxic effects by inhibiting mTORC1, blocking protein synthesis and cell-cycle progression within the tumor cell.[29,30,32,33] mTORC2 inhibitors are under clinical development (discussed below).

Mechanisms of Resistance to VEGFr-TKI Therapies

Shared mechanistic approaches between currently approved VEGF-targeted therapies have important clinical implications for development of cross-resistance. Most patients treated with VEGF-targeted therapies show transient

Table 2. Select Ongoing Clinical Studies in mRCC

ClinicalTrials.gov Identifier	Treatment Groups	Study Design	Estimated Completion Date*
NCT00720941	Pazopanib vs sunitinib (COMPARZ)	Phase III, randomized, open-label; no previous systemic treatment for mRCC	December 2012
NCT01030783	Tivozanib vs sorafenib (TIVO-1)	Phase III, randomized, open-label; treatment naïve or previous treatment with ≤1 systemic therapy (not including VEGFr-TKI or mTOR inhibitors)	June 2013
NCT00903175	Everolimus → sunitinib versus sunitinib → everolimus (RECORD-3)	Phase II, randomized, open-label; no previous systemic treatment	†December 2012
NCT00732914	Sorafenib → sunitinib vs sunitinib → sorafenib (SWITCH)	Phase III, randomized, open-label; no previous systemic treatment	November 2013
NCT00474786	Temsirolimus vs sorafenib (INTORSECT)	Randomized, open-label; refractory to first-line sunitinib	May 2014
NCT01491672	Everolimus (RECORD-4)	Phase II, open-label; post-relapse on first-line sunitinib, other anti-VEGF therapy, or cytokine therapy	November 2013
Australian New Zealand Clinical Trials Registry	Everolimus alternating with sunitinib in repeated 12-week treatment cycles (EVERSUN)	Phase II, single-arm, nonrandomized, open-label, 2-stage study; no previous targeted therapy	
NCT01223027	Dovitinib (TKI258) vs sorafenib	Phase III, open-label, randomized; refractory to VEGF-based targeted therapy (eg, sunitinib, pazopanib, axitinib, tivozanib, bevacizumab) and mTOR inhibitor therapy (everolimus, temsirolimus, or ridaforolimus)	January 2014
NCT00719264	Everolimus + BEV vs INF-α + BEV (RECORD-2)	Phase II, randomized, open-label; no previous systemic treatment	April 2013
NCT00631371	BEV + temsirolimus vs BEV + IFN-α (INTORACT)	Phase IIIb, randomized, open-label; no previous systemic treatment	December 2013
NCT01198158	Everolimus + BEV vs everolimus + placebo	Phase III, randomized, double-blind; refractory to VEGFr-TKI therapy	†June 2019

*Per ClinicalTrials.gov, January 2013; †Estimated primary completion date (final data collection date for primary outcome measure), per ClinicalTrials.gov, January 2013.

IFN-α=interferon alfa; mRCC=metastatic renal cell carcinoma; mTOR=mammalian target of rapamycin; VEGF=vascular endothelial growth factor; VEGFr-TKI=vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

improvement (ie, tumor stasis or shrinkage) but ultimately develop resistance (typically within months), regardless of initial response.[15,16] Relapse (also termed "evasive resistance") is thought to occur through escape mechanisms that allow for continued angiogenesis despite VEGF signaling blockade, including activation/upregulation of alternative proangiogenic pathways (within the tumor itself and through recruitment of proangiogenic cells from the bone marrow), increased non–VEGF-based support of tumor vasculature through recruitment of pericytes, and enhanced aggressiveness of migration into normal cells.[34]

Data for tumor upregulation of non-VEGF angiogenic factors as underlying mechanisms of resistance con-

tinue to emerge. In a xenograft mouse model, increased expression of the proangiogenic cytokine interleukin-8 (IL-8) was demonstrated in sunitinib-resistant tumors.[35] Similarly, high baseline levels of IL-6 in patients with mRCC treated in phase III trials of pazopanib were associated with poorer prognosis (shorter median PFS) compared with low baseline IL-6 levels.[36] In experimental animal models and patients with cancer, persistence of myeloid-derived suppressor cells within tumors is another potential mechanism underlying antitumor immunity and subsequent tumor growth.[37] Additionally, fibroblast growth factor (FGF) is an alternative proangiogenic and tumor-promoting signaling pathway that

may play a role in resistance to VEGF blockade.[38,39] In a mouse model, hypoxia-induced upregulation of FGF has been reported to stimulate tumor angiogenesis in a VEGF-independent manner.[40]

No single agent provides complete therapeutic blockade of all angiogenic signaling cascades, and hypoxia induced by VEGF blockade triggers signaling pathways that result in enhanced tumor aggressiveness and metastasis.[41]

Ongoing Clinical Trials in mRCC

Current treatment strategies involve sequential administration of monotherapies with the goal of prolonging patient survival while limiting toxicities associated with combination therapy. Given the potential for cross-resistance of agents within the same mechanistic class, interest in sequential therapy that incorporates agents with different mechanisms of action (MOAs) is growing.

Several recently completed and ongoing clinical trials are testing various approaches to mRCC treatment to determine whether there is an optimal sequence of targeted agents and if combination therapy with targeted agents benefits patients with mRCC. Highlights of key trials are presented in Table 1 (completed trials) and Table 2 (ongoing trials) and are discussed next.

Sequential Monotherapy
First Line
• **COMPARZ: Pazopanib Versus Sunitinib**
• **TIVO-1: Tivozanib Versus Sorafenib**
Two ongoing, phase III, open-label, head-to-head studies are comparing different VEGFr-TKIs as first-line therapies for mRCC. COMPARZ (A Study of Pazopanib Versus Sunitinib in the Treatment of Subjects With Locally Advanced and/or Metastatic Renal Cell Carcinoma) evaluates the efficacy and safety of pazopanib compared with sunitinib.[42] TIVO-1 (A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib [AV-951] to Sorafenib in Subjects With Advanced Renal Cell Carcinoma) compares the efficacy and safety of the investigational agents tivozanib and sorafenib (NCT01030783).[43] PFS is the primary endpoint in both trials.

Because sunitinib and pazopanib have received level 1 recommendations as first-line treatment,[19] COMPARZ should further guide treatment decisions regarding optimal selection of a first-line VEGFr-TKI. Recent results of PISCES (Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer) may also guide treatment decisions in this setting. In this study, significantly more treatment-naïve patients preferred pazopanib over sunitinib because of better general quality of life and less fatigue; pazopanib was also preferred over sunitinib by physicians.[44]

Top-line findings from TIVO-1 were released in January 2012. In the prespecified subpopulation of treatment-naïve patients (~70% of the total population), tivozanib significantly improved PFS compared with sorafenib; median PFS was 12.7 and 9.1 months, respectively.[45] These positive findings may result in the introduction of tivozanib as another therapeutic option for treatment-naïve patients with mRCC. They also provide evidence on the use of sorafenib in treatment-naïve patients; at present, this has a level 1 recommendation only as second-line therapy after previous treatment with cytokines.[19]

First- and Second-Line Sequencing
• **RECORD-3: Everolimus → Sunitinib OR Sunitinib → Everolimus**
• **SWITCH: Sunitinib → Sorafenib OR Sorafenib → Sunitinib**
Currently, key areas of focus in the treatment of mRCC include optimal sequencing of targeted agents and therapeutic cross-resistance. Various strategies for sequencing first- and second-line therapies are under investigation in prospective studies, including those using agents with the same MOA (eg, VEGFr-TKI → VEGFr-TKI) and those that incorporate agents with distinct MOAs (eg, mTOR → VEGFr-TKI).

The RECORD (Renal Cell Cancer Treatment With Oral RAD001 Given Daily)-3 study is a phase II, open-label, randomized trial evaluating the efficacy of everolimus (first-line) → sunitinib (second-line) versus sunitinib (first-line) → everolimus (second-line).[46] Sunitinib currently has a level 1 recommendation for first-line treatment, and both agents have level 1 recommendations for second-line treatment.[19] RECORD-3 will provide the first head-to-head comparison of a VEGFr-TKI and an mTOR inhibitor as first-line treatment for mRCC and will yield prospective data for everolimus as second-line treatment after exclusive use of sunitinib. The SWITCH (Efficacy and Safety of Sorafenib Followed by Sunitinib Versus Sunitinib Followed by Sorafenib in the Treatment of First-Line Advanced mRCC) study is a phase III randomized trial evaluating the optimal first-/second-line sequence of sunitinib and sorafenib (NCT00732914).[47] This trial will provide valuable prospective data about the safety and efficacy of sequential VEGFr-TKI → VEGFr-TKI therapy. Recently reported preliminary results demonstrated that rates of AEs were higher with a first-line VEGFr-TKI than with a second-line VEGFr-TKI with typical AE profiles observed for both individual agents.[48] Together, results from these studies are expected to enable better-informed treatment decisions, particularly for selection of second-line therapy after first-line sunitinib failure.

Second Line
- **TIVO-1: Tivozanib Versus Sorafenib (after relapse on cytokine therapy)**
- **AXIS: Axitinib Versus Sorafenib (after relapse on cytokine or VEGF-targeted therapy)**
- **Temsirolimus Versus Sorafenib (after relapse on sunitinib)**
- **RECORD-4: Everolimus (after relapse on sunitinib, other VEGF-targeted therapy, or cytokine treatment)**
- **EVERSUN: Alternating Sunitinib → Everolimus (before development of relapse)**

Efficacy and safety of targeted agents for second-line treatment are being evaluated in several monotherapy studies, including some designed to directly compare VEGFr-TKI versus VEGFr-TKI or mTOR inhibitor versus VEGFr-TKI after disease progression on previous therapy.

In addition to assessing first-line treatment as discussed, TIVO-1 (tivozanib vs sorafenib) will provide data about the efficacy and safety of these therapies in a second-line setting because patients who received no more than 1 prior cytokine-based therapy are eligible. Preliminary results demonstrated that in the overall study population, PFS was significantly improved with tivozanib compared with sorafenib; median PFS was 11.9 and 9.1 months, respectively.[49] The safety profile of tivozanib in this trial was consistent with findings from phase II studies; hypertension was the most commonly reported AE.

Final results of the phase III randomized AXIS (Axitinib [AG 013736] as Second-Line Therapy for Metastatic Renal Cell Cancer) trial[17] led to its recent FDA approval for patients with mRCC.[6] In the AXIS trial, patients who progressed on first-line treatment with sunitinib, cytokine-based therapy, bevacizumab plus IFN-α, or temsirolimus were randomly assigned to receive axitinib or sorafenib. PFS (per independent review assessment) was 6.7 months with axitinib and 4.7 months with sorafenib (stratified hazard ratio [HR], 0.665; 95% confidence interval [CI], 0.544–0.812; $P<.0001$). About one-third of patients (35%) received previous cytokine therapy; thus, the AXIS study represented their first exposure to a VEGFr-TKI. In this cytokine-refractory subgroup, median PFS was 12.1 months for axitinib and 6.5 months for sorafenib. About one-half of patients (54%) had previously received sunitinib as first-line therapy. In this sunitinib-refractory subgroup, median PFS was lower: 4.8 months with axitinib and 3.4 months with sorafenib. The objective response rate in the total study population was higher for axitinib (19%) than for sorafenib (9%; $P=.0001$). Both treatment arms had a generally similar safety profile. Select AEs occurring more commonly with axitinib versus sorafenib were all-grade hypertension (40% vs 29%), nausea (32% vs 22%), dysphonia (31% vs 14%), and creatinine level elevation (55% vs 41%). Conversely, AEs that were more common with sorafenib than with axitinib included hand-foot syndrome (51% vs 27%), alopecia (32% vs 4%), rash (32% vs 13%), anemia (52% vs 35%), hypophosphatemia (50% vs 13%), hypocalcemia (59% vs 39%), and lipase level elevation (46% vs 27%).

The ongoing phase III, randomized, open-label INTORSECT study will be the first study to provide head-to-head prospective data on the efficacy and safety of an mTOR inhibitor (temsirolimus) versus a VEGFr-TKI (sorafenib) in patients who failed a first-line VEGFr-TKI (sunitinib) (NCT00474786).[50] Recently reported topline results demonstrated that PFS was numerically, but not significantly, longer in patients treated with temsirolimus versus sorafenib; however, OS was significantly longer for patients treated with sorafenib.[51] In addition to providing insight into the benefits/risks of VEGFr-TKI → mTOR versus VEGFr-TKI → VEGFr-TKI sequencing, final results of this study will generate the first prospective data for temsirolimus as second-line therapy; temsirolimus currently has level 1 recommendations for use as first-line therapy in high-risk patients.[19]

RECORD-4 (NCT01491672) is a phase II open-label study of second-line everolimus in patients with mRCC who received first-line treatment for mRCC. Patients will be stratified according to first-line treatment with sunitinib, other anti-VEGF therapy, or cytokine therapy. The primary endpoint will be PFS.[52] Although everolimus currently has level 1 recommendations as second-line therapy after relapse on VEGFr-TKI treatment, most patients in the pivotal RECORD-1 study had received other previous treatment, in addition to a VEGFr-TKI.[14] The RECORD-4 study will enable evaluation of everolimus treatment in a purely second-line setting and may broaden the utility of everolimus as second-line treatment.

Another approach under investigation is based on the theory that switching to treatment with an alternate MOA before disease progression may increase the time to development of resistance and confer improved clinical benefit. Data from EVERSUN (A Phase 2 Trial of EVERolimus Alternating With SUNitinib as First-Line Therapy for Advanced Renal Cell Carcinoma) will provide intriguing insights into the development of resistance with an alternating VEGFr-TKI → mTOR inhibitor sequencing strategy. This phase II, single-arm, 2-stage trial is enrolling treatment-naïve patients with mRCC. Treatment will be given in 12-week cycles, composed of sunitinib (4 weeks on, 2 weeks off) and everolimus (5 weeks on, 1 week off).[53] Because target enrollment is only 55 patients, larger comparative studies, including inclusion of a standard-of-care treatment arm, will be required before changes to treatment algorithms can be considered.

Third Line
• Dovitinib Versus Sorafenib

No targeted agents are approved as third-line treatment of mRCC, as reflected by lack of guidance in this area in current clinical practice guidelines. This setting needs robust clinical data to help inform treatment decisions.

Dovitinib (TKI258) inhibits multiple angiogenic factors, including FGF receptor and VEGFr, and has shown efficacy in early-phase clinical trials in patients with mRCC previously treated with a VEGFr-TKI and/or an mTOR inhibitor.[54] Dovitinib is being evaluated in a phase III, randomized, open-label trial as third-line treatment versus sorafenib in patients who received treatment with 1 previous VEGF-targeted agent and 1 previous mTOR inhibitor.[55] Results should provide guidance about the effectiveness of targeted therapy for mRCC in the third-line setting. The trial is scheduled to close to accrual in July 2012.

Combination Therapy
First Line
• RECORD-2: Bevacizumab Plus Everolimus Versus Bevacizumab Plus IFN-α
• INTORACT: Bevacizumab Plus Temsirolimus Versus Bevacizumab Plus IFN-α Second-Line (after relapse on VEGFr-TKIs)
• Everolimus Plus Bevacizumab Versus Everolimus Plus Placebo

Combination therapy could potentially improve prognosis for patients with mRCC. As demonstrated in other cancers, simultaneous intervention at multiple points in the pathologic processes of tumorigenesis is likely to yield greater levels of cytotoxicity while reducing the opportunity for resistance to develop. The combination of an mTOR inhibitor with a VEGFr-TKI is very appealing from a mechanistic perspective, allowing simultaneous targeting of angiogenesis and tumor cell growth.

The utility of combination therapy in the treatment of mRCC is being evaluated in randomized trials. Select studies in the first-line treatment setting include RECORD-2 and INTORACT (Investigation of Torisel and Avastin Combination Therapy). RECORD-2 is a phase II open-label study comparing bevacizumab plus IFN-α versus bevacizumab plus everolimus (NCT00719264).[56] INTORACT is a phase IIIb open-label study comparing bevacizumab plus temsirolimus versus bevacizumab plus IFN-α (NCT00631371).[57] In the second-line treatment setting, a randomized phase III trial is evaluating combination therapy for patients with mRCC who have progressed on VEGFr-TKI treatment. This trial, sponsored by the Cancer and Leukemia Group B (CALGB), is comparing everolimus plus bevacizumab versus everolimus plus placebo (NCT01198158).[58]

Early-phase studies of combination therapies, such as bevacizumab plus everolimus[59] and tivozanib plus temsirolimus[60] regimens, have shown promising tolerability profiles. In a phase Ib, open-label, dose-escalation trial in patients with mRCC, tivozanib in combination with temsirolimus was well tolerated.[60] The incidence of AEs observed with combination therapy was consistent with the safety profiles of each agent when used as monotherapy. No grade 4 events or dose-limiting toxicities were reported. However, substantial toxicity has been noted with other combinations, including bevacizumab plus temsirolimus,[61] bevacizumab plus sunitinib (particularly at higher sunitinib doses),[62] everolimus plus sunitinib,[63,64] and temsirolimus plus sunitinib.[65] Ongoing RECORD-2, INTORACT, and CALGB trials will further evaluate the viability of bevacizumab plus mTOR inhibitor combination therapy and will provide data that might enable a comparison of risks/benefits for combination versus sequential treatment strategies.

New Mechanistic Directions in mRCC Treatment

The quest for enhanced understanding of signaling pathways and resistance mechanisms involved in mRCC is leading to novel mechanistic approaches, including dual inhibition of PI3K and mTORC1/2 and inhibition of MET, VEGFR2, and the programmed death-1 co-inhibitory receptor (PD-1).

The critical role of PI3K/Akt in cell growth and survival makes this pathway an attractive target for anticancer therapy. Agents targeting the PI3K/Akt pathway are in clinical development, including the PI3K/mTORC1/2 dual inhibitor NVP-BEZ235[32] and the PI3K/Akt pathway inhibitor perifosine.[66] In a study by Cho and associates,[32] NVP-BEZ235 showed improved efficacy over rapamycin alone in a mouse xenograft model of RCC. In a phase I dose-escalation study in patients with advanced solid tumors, including renal, NVP-BEZ235 was well tolerated with a favorable safety profile.[67] A phase I/II open-label study of NVP-BEZ235 in patients with advanced solid tumors with molecular alterations in the PI3K pathway is ongoing.[68] Perifosine is being evaluated as second-line therapy in patients with advanced mRCC who have relapsed on prior treatment with sunitinib and/or sorafenib, and also as third-line therapy for patients who were previously treated with 1 VEGFr-TKI and 1 mTOR inhibitor.[66]

Inhibition of MET has been shown to overcome acquired resistance to anti-VEGF agents.[69] A recent phase I study demonstrated that cabozantinib (Cometriq, Exelixis), an inhibitor of MET and VEGFR2, may be an effective therapy for VEGF-refractory patients with mRCC.[70] In this study, 25 patients who previously failed treatment with up to 6 targeted agents were treated with

cabozantinib 140 mg daily. In this heavily pretreated population, objective response rate was 28% and median PFS was 14.7 months; median OS had not been reached with median follow-up of 14.7 months. Among patients with bone metastases (16%), some experienced bone lesion resolution and pain relief with cabozantinib treatment.

In RCC, PD ligand-1 (PD-L1) expression on tumor cells has been associated with more aggressive disease and shorter survival.[71] Inhibition of PD-1, which is expressed by activated T cells, may be an important new target for RCC immunotherapy. In a phase I study, 33 patients with RCC were treated with BMS-936558, a human monoclonal antibody that inhibits PD-1, via IV administration every 2 weeks (10 mg/kg, n=16; 1 mg/kg, n=17).[72] All patients had previously received treatment; 74% previously received antiangiogenic agents. The toxicity profile was consistent with that reported for immunotherapeutic agents; 18% of patients experienced grade 3 or grade 4 AEs. Clinical activity occurred at both doses; 9 patients had an objective response (PR, n=8, and CR, n=1), and PFS at 24 weeks was 56%. At the 10 mg/kg dose, approximately 70% of patients were progression-free at 24 weeks. Further development of BMS-936558 in patients with mRCC is ongoing.

Predictive Biomarkers

In tandem with investigation of various combinations of drug therapies and research into new mechanistic approaches, identification of predictive/prognostic biomarkers of disease progression continues. Such knowledge will ultimately help individualize therapy and enable risk/benefit decisions in clinical trials and daily practice. In a retrospective study evaluating prognostic factors in patients with mRCC who received VEGF-targeted therapy across 7 North American oncology treatment centers, factors associated with poor prognosis (per the Cox proportional hazards model) included Karnofsky performance status under 80%; less than 1 year in the time from diagnosis to treatment; hemoglobin level less than the lower limit of normal; and calcium level, neutrophil count, and platelet count greater than the upper limit of normal.[73]

Gene expression analysis evaluating molecular aspects of tumors that distinguish robust subsets of clear cell RCC (with a potential impact on prognosis) is an area of continuing research. Findings from Brannon and coworkers[74] suggest a more favorable survival prognosis for subtype ccA than for subtype ccB. Gordan and associates[75] characterized tumor samples of sporadic human clear-cell RCC based on VHL genotype and patterns of HIF-α expression. Findings revealed 3 distinct tumor phenotypes: wild-type VHL alleles and undetectable expression of HIF-α protein (VHL WT), VHL-deficient

tumors with detectable expression of HIF-1α and HIF-2α proteins (H1H2), and VHL-deficient tumors exclusively expressing HIF-2α (H2). Results showed differences in cell proliferation and oncogenic activity between groups. For instance, compared with H1H2 or VHL WT tumors, H2 tumors showed enhanced activity of the c-Myc oncogenic pathway and higher proliferation rates. Saez and colleagues demonstrated that, in patients with mRCC who were treated with first-line VEGFr-TKIs, unlike VHL status, positive expression (10% staining intensity) of H1 and H2 significantly correlated with PFS and OS, and that H1 was predictive for response rate.[76] Hudes and coworkers showed that gain of chromosome 5q and no loss of chromosome 14/14q in tumor DNA of patients with mRCC treated with pazopanib were associated with significantly longer PFS.[77] Rini and associates[78] noted a relationship between patient characteristics, VHL gene status, and clinical outcomes in patients with mRCC who were receiving VEGF-based therapies. Favorable prognosis (eg, longer time to progression [TTP]) was associated with male sex, higher baseline hemoglobin level, no hepatic metastases, and no previous radiation therapy. Results showed no impact of VHL mutations or methylation on overall tumor shrinkage or objective response; however, patients with VHL methylation or a mutation that truncated or shifted the VHL reading frame had longer TTP compared with patients without these features. Pomerantz and colleagues suggested that inherited variation at PIK3CA was associated with PFS and OS after mTOR inhibition, which was maintained when adjusted for age, sex, and Memorial Sloan-Kettering Cancer Center (MSKCC) risk stratification.[79]

Conclusion

Optimized sequential therapy and combination therapy represent 2 main areas of interest being evaluated in clinical trials of mRCC. Sequential treatment using agents with similar MOAs may lead to at least partial cross-resistance, resulting in impaired anticancer activity and ultimately to reduced patient survival. Ongoing clinical trials should help to establish the degree to which cross-resistance between agents occurs in clinical practice and to identify which agents, when used consecutively, are associated with the most favorable treatment outcomes. Agents with differing MOAs may decrease the potential for cumulative toxicity. Combination therapy holds the potential for improved anticancer activity compared with monotherapy. However, to date, the utility of this approach has generally been limited by toxicity. If a suitable combination can be found that provides improved efficacy with an acceptable risk/benefit ratio, this might herald a major advance in the treatment of mRCC.

In conclusion, intense efforts continue in the quest to establish optimized treatment regimens that offer improved survival, manageable safety, and the ability to tailor therapy to individual patient needs. Clinical trial data maturing in the next 1–2 years should provide insight regarding which sequences are safest and most effective, and should further elucidate the benefits/risks of combination therapy. It remains to be seen whether results of these studies will lead to a paradigm shift in treatment recommendations for patients with mRCC.

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