REVIEW ARTICLE

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Systemic Therapy for Metastatic Renal-Cell Carcinoma

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Until recently, there was a dearth of effective systemic therapies for kidney cancer. The incidence of the disease steadily increased from 1975 through 2008 and leveled off after 2008.[1-3] Currently, it is among the 10 most frequently diagnosed cancers in men and women in the United States, with more than an estimated 62,000 new cases in 2016.[4] The prognosis has historically been poor, with current 5-year survival rates of 74% overall, decreasing to 53% among patients with locoregional (stage III) disease and 8% among patients with metastatic disease.[1,3] Kidney cancer is a disease of the middle-aged and elderly: 91% of patients receive a diagnosis at 45 years of age or older, and 48% receive a diagnosis at 65 years of age or older.[1] Renal-cell carcinoma, the most common form of kidney cancer, occurs in 90% of cases and is nearly twice as common in men as in women.[3]

The 5-year survival rate among patients with kidney cancer increased from 57% in 1987–1989 to 74% in 2006–2012[1]; this increase was attributable in part to a higher proportion of indolent and low-stage tumors identified using improved early-detection techniques.[5] Still, one third of patients with kidney cancer present with regional or distant metastases,[1] and of patients with localized renal-cell carcinoma treated with nephrectomy with curative intent, approximately one quarter have relapses in distant sites.[6-8] Distant metastases occur most often in the lungs, lymph nodes, liver, bone, and brain.[9] Although more than 14,000 patients die from kidney cancer each year,[4] we have seen considerable progress in the systemic treatment of metastatic renal-cell carcinoma in the past 20 years.[10] Researchers have achieved a better understanding of the pathogenesis of the most common type of renal-cell carcinoma, clear-cell renal-cell carcinoma. This understanding has led to new agents, expanded treatment options, and increased rates of survival.

Biologic and Pathological Characteristics and the Genomic Landscape

Renal-cell carcinoma, which consists of a heterogeneous group of cancers arising from the nephron, has various histologic and molecular subtypes. The most recent pathological classification of renal-cell tumors, which takes molecular characteristics into account, is the Vancouver Classification of Renal Neoplasia by the International Society of Urological Pathology.[11] Most data on overall treatment outcomes are from studies involving patients with clear-cell renal-cell carcinoma, which makes up approximately 70% of renal-cell carcinomas.[3] Clear-cell renal-cell carcinoma is associated with mutations in *VHL*, an essential component of the cellular oxygen-sensing pathway.[12] *VHL* is located on chromosome 3p and is inactivated by mutation in 52% of clear-cell renal-cell carcinomas.[13] In normal cells,

the *VHL*-containing complex targets hypoxia-inducible factor for degradation. However, in clear-cell renal-cell carcinoma, this complex is dysfunctional and hypoxia-inducible factor accumulates in the cell and activates many downstream hypoxia-driven genes, including vascular endothelial growth factor (*VEGF*) and other genes involved in angiogenesis, cell growth, and survival.[14] The treatment of renal-cell carcinoma has been transformed by achievement of a basic understanding of these events. This understanding has led to the development of new antiangiogenic drugs that target VEGF or its receptors.

New genomic techniques, including next-generation sequencing, have revealed the large spectrum of genetic and epigenetic changes in kidney cancers. Studies of clear-cell renal-cell carcinoma from the Cancer Genome Atlas (TCGA) Research Network and other studies have shown mutations in several other genes, albeit at lower frequencies than *VHL*; these genes include *PBRM1* (40%), *SETD2* (15%), and *BAP1* (15%),[13,15,16] which are all part of the chromatin remodeling–histone methylation pathway. Like *VHL*, these three genes are located within a 50-Mb region on the short arm of chromosome 3p. One of these mutations, *BAP1*, has been associated with shorter survival.[17]

TCGA analyses have also identified multiple components of the intracellular mechanistic target of rapamycin (mTOR) pathway that were altered in a subset of clear-cell renal-cell carcinomas; these alterations provide a rationale for the study of mTOR inhibitors.[13] Activation of the mTOR pathway leads to increased cell growth and division,[18] and studies have shown clinical responses to mTOR inhibitors in many diseases driven by this pathway.[19]

Papillary renal-cell carcinoma is the second most common histologic subtype, comprising 10% of renal-cell carcinomas.[3,20] The most common copy-number events are gain of chromosome 7 (where *MET* is located) and chromosome 17.[21] Alterations in *MET* are associated with type 1 papillary renal-cell carcinoma, whereas type 2 papillary renal-cell tumors are characterized by alterations of the NRF2–antioxidant response element.[21] Rarer types of renal-cell carcinoma include chromophobe tumors (in ≤5% of cases), collecting-duct carcinoma and renal medullary carcinoma (each in <1% of cases), and translocation carcinoma (in <1% of cases).[3,22] Two genes are mutated in chromophobe tumors: *TP53* in 32% of cases and *PTEN* in 9%.[23] There is frequent loss of *CDKN2A* (a cyclin-dependent kinase inhibitor) expression in collecting-duct carcinoma[24] and loss of expression of *SMARCB1* (*INI1*), a component of chromatin-remodeling complexes, in renal medullary carcinoma.[25] Translocation carcinoma may involve *TFE3* or *TFEB* gene fusions (chromosomal gain of 17q, 44%).[26]

There has also been a resurgence of interest in cancer immunotherapy with the development of immune checkpoint inhibitors, which block antibodies directed against the programmed cell death protein 1 (PD-1) receptor or its ligand 1 (PD-L1). PD-L1 binding to PD-1 negatively regulates the immune response, inhibiting cytokine release and the cytotoxic activity of antitumor T cells.[27] Most renal-cell carcinomas express PD-L1, and multiple series of studies involving patients with clear-cell renal-cell carcinoma[28] and patients with non–clear-cell renal-cell carcinoma[29] have shown PD-L1 expression on the tumor-cell membrane and in tumor-infiltrating mononuclear cells.[28,29] These features, coupled with the fact that renal-cell carcinoma is sensitive to immunotherapy, as evidenced by observed responses to cytokines (interleukin-2 and interferon) in a fraction of patients,[30] justify the study of blocking antibodies directed against PD-1–PD-L1 in this disease. Figure 1 summarizes therapeutic biologic targets and targeted drugs that have received regulatory approval for use in patients with metastatic renal-cell carcinoma.

HISTORICAL PERSPECTIVE AND PROGNOSTIC FACTORS IN METASTATIC DISEASE

Hormonal therapy and cytotoxic chemotherapy have little to no activity in metastatic renal-cell carcinoma. Interferon alfa was the mainstay of treatment until 10 years ago, but it had a low response rate of 12% and a high level of toxicity.[10] High-dose interleukin-2 was reported to achieve a complete response in 5% of patients with advanced renal-cell carcinoma; many of these responses were durable.[31] However, high-dose interleukin-2 is associated with severe cardiovascular toxicity, and it is used only in hospitals that can provide sufficient supportive care measures to manage the acute toxic effects.[32] A contemporary study involving 120 patients did not validate predictive bio-

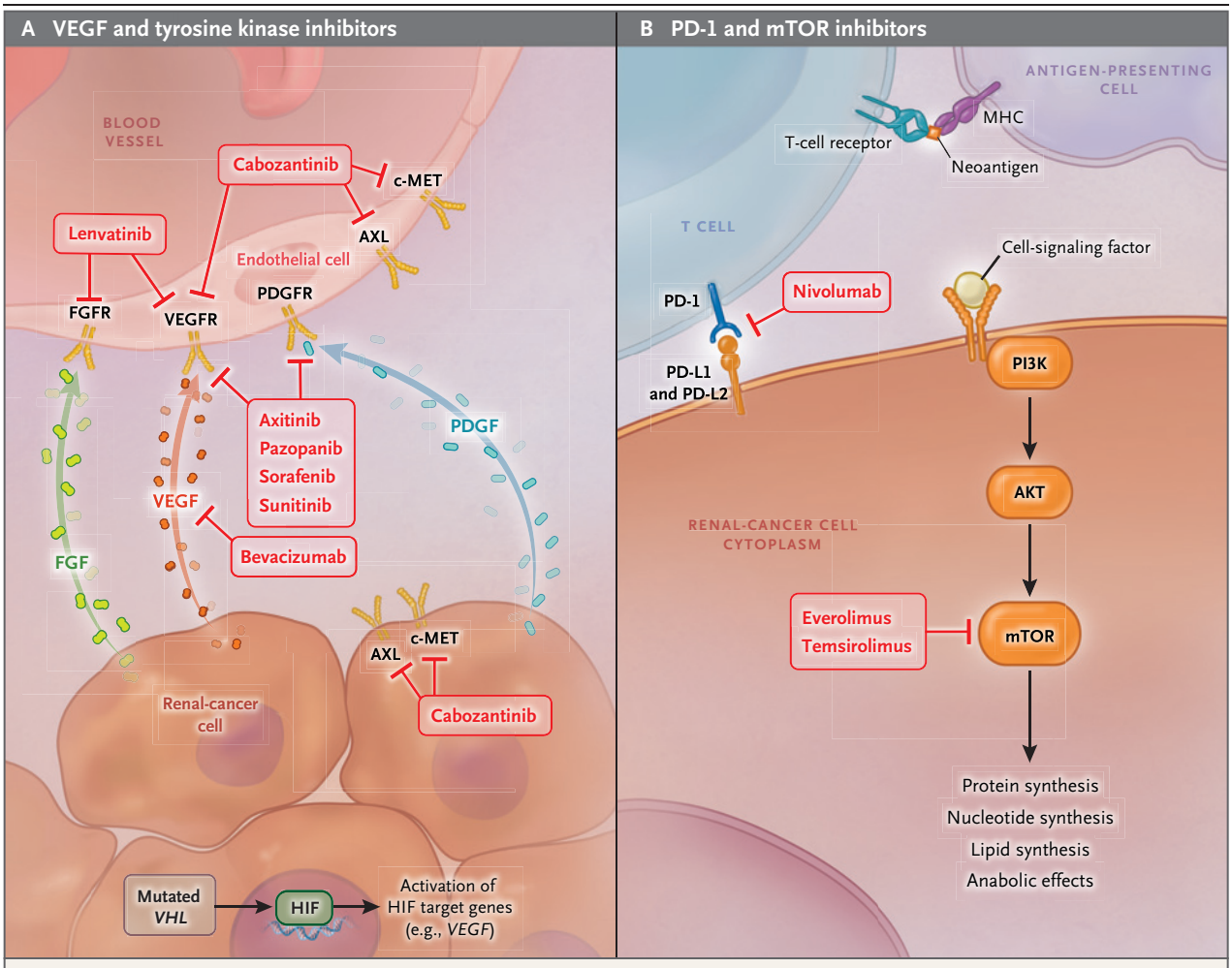

Figure 1. Pathways and Current Drugs in Metastatic Renal-Cell Carcinoma.

In Panel A, a renal-cancer cell and an endothelial cell are shown in relation to vascular endothelial growth factor (VEGF) and tyrosine kinase inhibitors. When *VHL* is mutated, accumulated hypoxia-inducible factor (HIF) translocates into the nucleus, leading to transcription of a large number of hypoxia-inducible genes, including *VEGF*. FGF denotes fibroblast growth factor, FGFR FGF receptor, PDGF platelet-derived growth factor, PDGFR PDGF receptor, and VEGFR VEGF receptor. In Panel B, blockade of programmed cell death protein 1 (PD-1) by nivolumab (top) results in reactivation of T-cell–mediated tumor-cell killing. Everolimus and temsirolimus (bottom) inhibit the mechanistic target of rapamycin (mTOR) complex 1, leading to several downstream antineoplastic effects. Drug options are listed alphabetically. MHC denotes major histocompatibility complex, PD-L1 PD-1 ligand 1, PD-L2 PD-1 ligand 2, and PI3K phosphatidylinositol 3-kinase.

markers of response and thus could not clarify which patients are most likely to have a response.[33]

Certain clinical factors associated with a reduced rate of overall survival have been incorporated into prognostic risk models. These models categorize patients according to anticipated survival and help in clinical trial design and interpretation and in counseling of individual patients. The most widely used prognostic model, developed by investigators at Memorial Sloan Kettering Cancer Center, is based on results from immunotherapy trials.[34] This model incorporates five factors that have been shown to correlate with a decreased rate of survival among patients with advanced renal-cell carcinoma: poor performance status, a high serum lactate dehydrogenase level, a high serum calcium level, a low hemoglobin concentration, and less than a 1-year interval from diagnosis to treatment. The median survival among patients with none of these risk factors (the favorable-risk group) was significantly higher than among patients with one or

two risk factors (the intermediate-risk group) and among those with three or more risk factors (the poor-risk group) (30 months vs. 14 months vs. 5 months; P<0.001). A model described by Hudes et al. added a sixth risk feature (more than one site of metastases) to the five risk factors; these criteria were used to select patients who had a poor prognosis to receive temsirolimus mTOR inhibitor therapy, interferon alfa, or both in a randomized trial.[35]

The criteria of the International Metastatic Renal Cell Carcinoma Database Consortium were developed on the basis of data from patients who received VEGF-targeted therapies. This model incorporated four of the five adverse prognostic factors from the Memorial Sloan Kettering model, with two factors (high absolute neutrophil count and high platelet count) replacing lactate dehydrogenase levels.[36] In an updated study involving more than 1000 patients, median survival was 43 months in the favorable-risk group, 22 months in the intermediate-risk group, and 8 months in the poor-risk group.[37]

SYSTEMIC THERAPY FOR METASTATIC RENAL-CELL CARCINOMA

CLEAR-CELL RENAL-CELL CARCINOMA

In the past 10 years, treatment options for metastatic kidney cancer have been expanded. Interferon alfa has been replaced by therapies with higher rates of response, longer progression-free survival, or both. These therapies, including antiangiogenic drugs targeting VEGF and its receptors, mTOR inhibitors, and an immune checkpoint inhibitor, have improved clinical outcomes and expanded treatment options in this difficult-to-treat cancer (Table 1). In 2005 and 2006, the Food and Drug Administration (FDA) approved sorafenib and sunitinib. The approval of five other antiangiogenic drugs (pazopanib, axitinib, bevacizumab, cabozantinib, and lenvatinib) followed. Two mTOR inhibitors, temsirolimus and everolimus, and the immune checkpoint inhibitor nivolumab showed benefit in randomized, phase 3 trials and were also approved by the FDA.

Treatment choices are evidence-based and are guided by the results of randomized, phase 3 trials. Several drugs to treat renal-cell carcinoma, including interleukin-2, sunitinib, and lenvatinib (in combination with everolimus), also have been approved on the basis of positive results of phase 2 trials. Eligibility for these trials differs according to the degree and type of therapy previously received. Treatments are also selected on the basis of individual patient factors, which are influenced by coexisting conditions and the toxicity profiles of specific agents (Table 2). For example, hyperglycemia is a class effect of mTOR inhibitors, and therefore an antiangiogenic drug might be selected over everolimus for a patient with difficult-to-manage diabetes. The checkpoint inhibitor nivolumab is avoided in patients with active autoimmune disorders. Figure 2 shows our proposed decision-making strategy for the treatment of patients with metastatic clear-cell renal-cell carcinoma according to the results of randomized trials. Since not all of the drugs have been compared with each other, there are several options for both first-line and second-line therapy according to the preference of the treating physician and the patient.[59]

FIRST-LINE OPTIONS

Sunitinib and pazopanib are oral multitargeted drugs against the VEGF receptors (VEGFRs) 1, 2, and 3, platelet-derived growth factor receptors, and other tyrosine kinases. Sunitinib has been associated with higher response rates and longer progression-free survival than interferon alfa,[38,39] and pazopanib has been associated with higher response rates and longer progression-free survival than placebo[40,41]; they are commonly used first-line agents (Table 1). Bevacizumab plus interferon alfa has been associated with a higher response rate and longer progression-free survival than interferon alfa alone, but it retains the disadvantage of interferon alfa–related toxic effects such as fatigue.[42-45]

In a phase 3 trial of sunitinib versus pazopanib as first-line treatment, pazopanib was noninferior to sunitinib with respect to progression-free survival.[46] Similar outcomes with respect to overall survival were reported in the final analysis, with median survival approaching 30 months in both groups (Table 1).[47] Although pazopanib was associated with a higher incidence of hepatic toxicity (increased levels of alanine aminotransferase [all grades] in 60% of patients in the pazopanib group vs. 43% in the sunitinib group), sunitinib was associated with a higher incidence of fatigue (all grades, 63% vs. 55% in patients who received pazopanib), hand–foot syndrome (all grades, 50% vs. 29%), and thrombocytopenia (all

Table 1. Randomized Trials of Established Systemic Agents in Metastatic Clear-Cell Renal-Cell Carcinoma.*

Reference and Agents	Patients	Median Progression-free Survival	Hazard Ratio for Disease Progression (95% CI)	P Value	Median Overall Survival	Hazard Ratio for Death (95% CI)	P Value	Objective Response Rate
	no.	*mo*			*mo*			*percent*
First-line treatment								
Motzer et al.[38,39]†								
Sunitinib	375	11			26.4			31
Interferon alfa	375	5	0.42 (0.32–0.54)	<0.001	21.8	0.82 (0.67–1.00)	0.05	6
Sternberg et al.[40,41]†								
Pazopanib	290	9.2			22.9			30
Placebo	145	4.2	0.46 (0.34–0.62)	<0.001	20.5	0.91 (0.71–1.16)	0.22	3
Escudier et al.[42,43]								
Bevacizumab–interferon alfa	327	10.2			23.3			31
Interferon alfa	322	5.4	0.61 (0.51–0.73)	<0.001	21.3	0.86 (0.72–1.04)	0.13	13
Rini et al.[44,45]								
Bevacizumab–interferon alfa	369	8.5			18.3			26
Interferon alfa	363	5.2	0.71 (0.61–0.83)	<0.001	17.4	0.86 (0.73–1.01)	0.07	13
Motzer et al.[46,47]†								
Sunitinib	553	9.5			29.1			25
Pazopanib	557	8.4	1.05 (0.90–1.22)	NR	28.3	0.92 (0.79–1.06)	0.24	31
Hudes et al.[35],† Pfizer[48]								
Temsirolimus	209	5.5	0.66 (0.53–0.81)	<0.001‡	10.9	0.73 (0.58–0.92)	0.008‡	8.6
Temsirolimus–interferon alfa	210	4.7	NR	NR	8.4	0.96 (0.76–1.20)	0.70§	8.1
Interferon alfa	207	3.1	—	—	7.3	—	—	4.8

Second-line or later treatment								
Motzer et al.[49,50]†								
Everolimus	272	4.9			14.8			1.8
Placebo	138	1.9	0.33 (0.25–0.43)	<0.001	14.4	0.87 (0.65–1.15)	0.16	0
Escudier et al.[51,52]†								
Sorafenib	451	5.5			17.8		0.15	2
Placebo	452	2.8	0.44 (0.35–0.55)	<0.01	15.2	0.88 (0.74–1.04)		0
Rini et al.[53]†								
Axitinib	361	6.7			20.1			19
Sorafenib	362	4.7	0.66 (0.55–0.81)	<0.001	19.2	0.97 (0.80–1.17)	0.37	9
Motzer et al.[54,55]¶								
Lenvatinib–everolimus	51	12.8	0.45 (0.22–0.79)	0.003	25.5	0.51 (0.3–0.88)	0.02	35
Lenvatinib	52	9.0	0.62 (0.37–1.04)	0.12	19.1	0.68 (0.41–1.14)	0.12	39
Everolimus	50	5.6	—	—	15.4	—	—	0
Choueiri et al.[56,57]†								
Cabozantinib	330	7.4			21.4			17
Everolimus	328	3.9	0.51 (0.41–0.62)	<0.001	16.5	0.66 (0.53–0.83)	0.003	3
Motzer et al.[58]								
Nivolumab	406	4.6			25.0			25
Everolimus	397	4.4	0.88 (0.75–1.03)	0.11	19.6	0.73 (0.57–0.93)‖	0.002	5

* CI denotes confidence interval, dashes comparison values, and NR not reported.
† An independent radiology review was conducted.
‡ This P value is for the comparison of temsirolimus with interferon alfa.
§ This P value is for the comparison of temsirolimus–interferon alfa with interferon alfa alone.
¶ This was a phase 2 trial.
‖ A 98.5% confidence interval was used for the hazard ratio for death in this trial.

Table 2. Selected Toxic Effects from Approved Systemic Therapies in Advanced Renal-Cell Carcinoma.

Class and Drug*	Toxic Effects
VEGF ligand antibody: bevacizumab	Hypertension, proteinuria, impaired wound healing, gastrointestinal perforation
Tyrosine kinase inhibitor: axitinib, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib	Fatigue, hypertension, oral and gastrointestinal side effects (mucositis, dysphonia, nausea, vomiting, stomatitis, dysgeusia, diarrhea), skin problems (rash, hand–foot skin reactions), hair loss and changes in hair color, weight loss, cytopenias, hypothyroidism, elevated liver-function values
Mechanistic target of rapamycin inhibitor: everolimus, temsirolimus	Fatigue, nausea, rash, pulmonary side effects (cough, dyspnea, pneumonitis), diarrhea, infections, peripheral edema, anemia, hyperlipidemia, hyperglycemia
Programmed death-1 inhibitor: nivolumab	Fatigue, nausea, diarrhea,† skin problems (pruritus, rash),† hypothyroidism,† pulmonary side effects (cough, dyspnea, pneumonitis),† elevated liver-function values,† other uncommon immune-related events

* Drug options are listed alphabetically.
† This toxic effect may have an immune-mediated cause.

grades, 78% vs. 41%).[46] The sunitinib-related toxic effects had a greater effect on activities of daily living, as reflected by patient-assessed health-related quality of life, which overall favored pazopanib.[46]

Intravenous temsirolimus, which is administered weekly, acts as a competitive inhibitor of mTOR complex 1. Temsirolimus is a first-line option in patients with poor-risk clear-cell renal-cell carcinoma, which constitutes 20% of all renal-cell carcinomas. This recommendation is based on the results of a randomized, phase 3 trial showing prolonged survival over interferon alfa among poor-risk patients selected according to the prognostic risk model described by Hudes et al.[35] Metabolic toxic effects, including hyperglycemia (all grades, 26%), hypercholesterolemia (all grades, 24%), and hyperlipidemia (all grades, 27%), were reported with temsirolimus and are class effects of mTOR inhibitors. Sunitinib and pazopanib have also been shown to achieve responses in poor-risk patients[36] and may be preferable to patients because of the oral route of administration.

SECOND-LINE AND LATER OPTIONS

Results of phase 3 trials provide support for the use of everolimus and axitinib as second-line treatments after first-line VEGF-targeted therapy (Table 1).[59] Everolimus is an orally administered mTOR inhibitor that was associated with longer progression-free survival than placebo in a randomized, phase 3 trial involving patients who had disease progression with sunitinib, sorafenib, or both.[49,50] Axitinib is an oral, potent inhibitor of VEGFRs that was associated with a longer progression-free survival than sorafenib among patients treated with one previous line of therapy (predominantly sunitinib and cytokines). The increase in progression-free survival with axitinib over sorafenib was smaller after first-line treatment with sunitinib than after first-line treatment with cytokines (median gain, 1.4 months vs. 5.6 months).[53]

Despite statistically and clinically significantly improved outcomes, resistance to both VEGF-targeted and mTOR-targeted therapies develops in nearly all patients. One strategy is to combine a VEGF and an mTOR inhibitor to delay the resistance that develops with single-agent therapy with either class. Bevacizumab plus temsirolimus or everolimus was compared with bevacizumab plus interferon alfa in three randomized trials, but no added efficacy was shown; one disadvantage was an increase in drug-related toxic effects.[60-62] However, a randomized, phase 2 study showed increases in progression-free and overall survival with the combination of everolimus with lenvatinib, a dual VEGFR–fibroblast growth factor receptor (FGFR) inhibitor, over everolimus alone (Table 1). Response rates were higher with the combination than with single-agent evero-

limus.[54,55] Dose reductions were performed often to alleviate toxicity, and the starting dose of each drug in the combination group was lower than the starting dose of lenvatinib or everolimus alone.

The mechanisms of acquired resistance to single-agent VEGF inhibitors remain largely unknown, although one potential mechanism is through alternative non-VEGF pathways involved in angiogenesis, invasion, and proliferation. Examples of such targets that are proposed to be involved in resistance to anti-VEGF therapy include the pathways for the tyrosine kinases FGFR, MET, and AXL.[63] Increased expression of MET and AXL has been implicated in the development of resistance to VEGFR inhibitors in preclinical models of renal-cell carcinoma.[64] In a phase 3 trial involving patients with disease that had progressed after first-line VEGF-targeted therapy, progression-free and overall survival were longer among patients who received cabozantinib, an inhibitor of VEGF receptors, MET, and AXL, than among those who received standard everolimus treatment (Table 1).[56,57] Dose reductions were more common with cabozantinib than with everolimus, but the rate of discontinuation of study treatment due to adverse events was similar in the two treatment groups.[56,57]

Nivolumab is a fully human monoclonal IgG4 antibody that is specific for PD-1. Cross-study comparison of data from early trials of this checkpoint inhibitor involving patients who had disease progression with VEGF-targeted agents showed responses and a longer overall survival among those who received nivolumab than among those who received everolimus.[65,66] A phase 3 trial involving patients with metastatic clear-cell renal-cell carcinoma showed longer overall survival and higher objective response rates among patients who received nivolumab than among those who received everolimus (Table 1), with lower rates of adverse events and improved quality of life.[58,67]

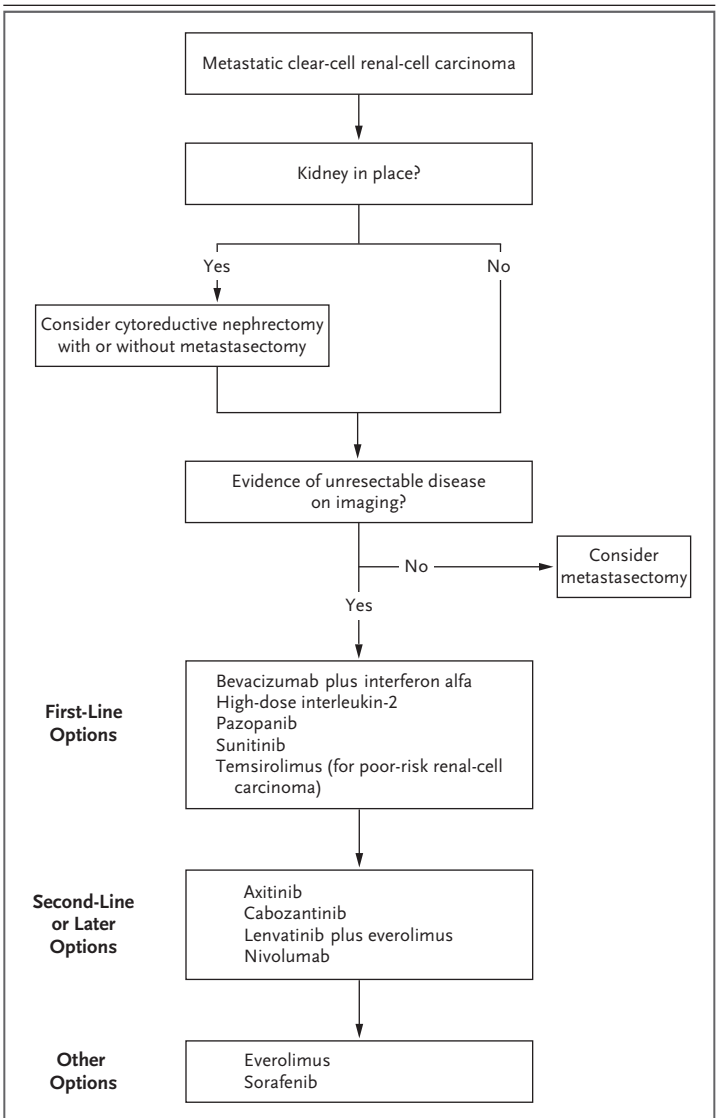

Figure 2. Proposed Decision-Making Strategy for the Treatment of Advanced Clear-Cell Renal-Cell Carcinoma.

Clinical trials are preferred for treatment when available. Drug options are listed alphabetically.

NON–CLEAR-CELL RENAL-CELL CARCINOMA

The histologic and molecular characteristics of non–clear-cell renal-cell carcinoma are different than those of clear-cell renal-cell carcinoma, but the general approach to treatment mirrors that for clear-cell renal-cell carcinoma. Since systemic treatments are generally less effective in patients with non–clear-cell renal-cell carcinoma and trial data regarding these patients are sparse, the National Comprehensive Cancer Network guidelines recommend enrolling patients in clinical trials for first-line systemic therapy.[59,68,69]

Three randomized, phase 2 trials compared sunitinib with everolimus in patients with non–clear-cell renal-cell carcinoma with various histologic characteristics (primarily the papillary cell

type). Sunitinib was associated with a trend toward longer progression-free survival than everolimus (8.3 vs. 5.6 months; 7.2 vs. 5.1 months; and 6.1 vs. 4.1 months).[70-72]

Altered *MET* status (mutation, splice variant, or gene fusion) or increased chromosome 7 copy number (on which *MET* is located) is present in a subset of the papillary cell type of renal-cell carcinoma.[21] Responses to drugs targeting the MET pathway have been observed in patients with papillary renal-cell carcinoma who have *MET* alterations; these findings provide a strong rationale for future biomarker-based studies of such agents.[73] In uncontrolled clinical trials, cytotoxic combination chemotherapy has been shown to produce clinical responses in patients with a specific diagnosis of collecting-duct renal-cell carcinoma or renal medullary carcinoma, or in those with renal-cell carcinoma with a predominance of sarcomatoid features.[74-79]

SURGERY AND RADIATION THERAPY IN ADVANCED RENAL-CELL CARCINOMA

Surgery plays a role in the management of metastatic renal-cell carcinoma. Cytoreductive nephrectomy is performed to remove the primary renal tumor in patients with known metastatic disease, and metastasectomy is performed to remove distant metastatic foci in some patients. Two randomized, phase 3 trials showed a survival advantage of cytoreductive nephrectomy over no surgery before patients received interferon alfa (11.1 months vs. 8.1 months, $P=0.05$; 17.0 months vs. 7.0 months, $P=0.03$).[80,81] Retrospective analyses based on large databases of results from patients who received VEGF-targeted and mTOR inhibitor drugs suggest a longer survival associated with cytoreductive nephrectomy than no surgery (17.1 months vs. 7.7 months, $P<0.001$).[82] Patients with good performance status and low systemic disease burden are candidates for cytoreductive nephrectomy.[83] In addition, surgical resection of metastatic foci is a treatment option in patients with a solitary metastasis.[84]

Although renal-cell carcinoma is a radioresistant tumor, radiation therapy can be used for palliation of symptoms, and up to 30% of patients with metastatic disease will receive radiotherapy for palliation of bone or brain metastases.[85] Clinical data show that in select cases, stereotactic ablative radiotherapy to a metastatic site results in local control with relatively minimal toxicity.[86] There is conflicting evidence about the effectiveness of bisphosphonates in patients with bone metastases.[87,88]

BIOMARKERS

Multiple candidates for predictive biomarkers from plasma, tumor, and host tissues have been explored in patients with metastatic renal-cell carcinoma who are receiving various systemic therapies, but none have been validated for clinical use.[89] Two retrospective studies have shown that mutations in elements of the mTOR pathway (*TSC1*, *TSC2*, and *MTOR*) are associated with an objective response to everolimus and temsirolimus[90,91]; this finding has also been noted in other cancer types.[92] In pretreatment samples, higher levels of tumor PD-L1 expression were associated with a reduced rate of survival among patients with renal-cell carcinoma who were receiving the PD-1 inhibitor nivolumab[58] (as well as VEGF-targeted agents[93]), but these data do not provide support for the use of PD-L1 as a predictive marker of a treatment benefit associated with nivolumab.

Tumor heterogeneity is a challenge that needs to be addressed before such markers can be identified and validated.[94] Intratumor heterogeneity can lead to an underestimation of the frequency of mutated genes; in one study, up to 69% of all somatic mutations varied according to biopsy site.[95]

FUTURE DIRECTIONS

Recent treatment strategies include the use of established drugs for new indications as well as new targeted agents. These strategies include drugs targeting mechanisms of resistance to antiangiogenic therapies (e.g., cabozantinib), carefully planned combinatorial approaches (e.g., lenvatinib plus everolimus), and new immune checkpoint blockers (e.g., nivolumab).

A randomized, phase 2 study involving patients with intermediate- and poor-risk clinical characteristics showed that cabozantinib was superior to standard sunitinib first-line treat-

Table 3. Selected Ongoing Phase 3 Trials of Combination Therapy with Immune Checkpoint Blockers and Vaccines as First-Line Treatment for Advanced Renal-Cell Carcinoma.

Treatment	Primary End Point	Estimated No. of Patients Enrolled	Trial	ClinicalTrials.gov No.
Pembrolizumab–lenvatinib vs. everolimus–lenvatinib vs. sunitinib	Progression-free survival	735	CLEAR	NCT02811861
Nivolumab–ipilimumab vs. sunitinib	Progression-free survival and overall survival	1070	CheckMate 214	NCT02231749
Atezolizumab–bevacizumab vs. sunitinib	Progression-free survival and overall survival in PD-L1–detectable tumors	900	IMmotion151	NCT02420821
Avelumab–axitinib vs. sunitinib	Progression-free survival	583	JAVELIN Renal 101	NCT02684006
Pembrolizumab–axitinib vs. sunitinib	Progression-free survival and overall survival	840	KEYNOTE-426	NCT02853331
Autologous dendritic-cell immunotherapy–sunitinib vs. sunitinib	Overall survival	450	ADAPT	NCT01582672

ment.[96] A large, phase 3 trial (ClinicalTrials.gov number, NCT02231749) comparing a combination of nivolumab and low-dose ipilimumab (a checkpoint blocker targeting cytotoxic T-lymphocyte antigen 4 [CTLA-4]) with sunitinib is under way. Other approaches combining anti-VEGF therapy with immune checkpoint blockers for first-line treatment are being tested as part of phase 3 trials. Table 3 summarizes some of the ongoing phase 3 pivotal trials of immune checkpoint blockers and vaccines involving patients with renal-cell carcinoma. These approaches could be a foundation to build on the next generation of clinical trials.

New drugs with new targets and mechanisms of action relevant to renal-cell carcinoma are needed. A major challenge remains the identification of tumor-specific biomarkers to predict a response to a specific agent; such biomarkers might allow for the rational design of the next generation of clinical trials.

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