

ADVANCED RENAL CELL CARCINOMA: A Clinical Update on Systemic Therapy

Introduction

Renal cell carcinoma (RCC) is the eighth most common cancer in the United States, with an estimated 76,080 new cases and 13,780 deaths for 2021.¹ Because early-stage RCC often goes undetected, approximately 16% of patients present with advanced RCC (aRCC),¹ which is defined as stage IV disease that may or may not include metastasis.² Moreover, an estimated one-third of patients presenting with early-stage resectable tumors will suffer recurrence.³ Systemic therapy is, therefore, crucial for controlling disease progression in advanced and relapsing disease. Fortunately, the number of effective therapies has rapidly expanded within the past decade, and the goal of therapy even with metastasis, is cure or long-term survival.⁴

Until 2005, the cytokines interferon- α (IFN- α) and high-dose interleukin-2 (IL-2) were the only treatments to show efficacy in a small group of patients.^{5,6} But as the role of angiogenesis in tumor growth became better understood, agents that target the vascular endothelial growth factor (VEGF) pathway replaced cytokines as the frontline treatment.⁶ Treatment options continued to evolve as therapies targeting the mechanistic (mammalian) target of rapamycin (mTOR) pathway and, more recently, immune checkpoint inhibitors (ICIs) and targeted agents improved patient outcomes. These therapies have transformed the systemic approach to aRCC in both treatment-naïve and previously treated patients.^{6,7} Treatment regimens are constantly evolving as data emerge from ongoing trials and guidelines change accordingly.

Risk stratification, which reflects patient outcomes in clinical trials, helps guide disease prognostication and patient counseling. Two prognostic models are used to stratify aRCC patients in clinical trials: the Memorial Sloan Kettering

Cancer Center model^{6,8,9} and the International Metastatic RCC Database Consortium (IMDC) model,^{6,10,11} both of which classify patients as favorable-, intermediate-, and poor-risk¹² (Table 1).

Table 1. Prognostic models for advanced RCC

RISK MODELS TO DIRECT TREATMENT	
Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model ^a	
Prognostic factors <ul style="list-style-type: none"> Interval from diagnosis to treatment of less than 1 year Karnofsky performance status less than 80% Serum lactate dehydrogenase (LDH) greater than 1.5 times the upper limit of normal (ULN) Corrected serum calcium greater than the ULN Serum hemoglobin less than the lower limit of normal (LLN) 	Prognostic risk groups <ul style="list-style-type: none"> Low-risk group: no prognostic factors Intermediate-risk group: one or two prognostic factors Poor-risk group: three or more prognostic factors
International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria ^b	
Prognostic factors <ol style="list-style-type: none"> Less than one year from time of diagnosis to systemic therapy Performance status <80% (Karnofsky) Hemoglobin < lower limit of normal (Normal: 120 g/L or 12 g/dL) Calcium > upper limit of normal (Normal: 8.5–10.2 mg/dL) Neutrophil > upper limit of normal (Normal: 2.0–7.0×10⁹/L) Platelets > upper limit of normal (Normal: 150,000–400,000) 	Prognostic risk groups <ul style="list-style-type: none"> Favorable-risk group: no prognostic factors Intermediate-risk group: one or two prognostic factors Poor-risk group: three to six prognostic factors

^a Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 2002;20:289-296.

^b Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. *J Clin Oncol* 2009;27:5794-5799.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Guidance on systemic therapy

Systemic therapy for clear cell aRCC, which accounts for 75%-85% of cases of RCC,⁴ is initiated promptly in patients with substantial disease burden¹³ according to the National Comprehensive Cancer Network Guidelines (NCCN) (Table 2), and participation in clinical trials is encouraged when feasible. Systemic therapy for the less common non-clear cell aRCC depends on the tumor's histologic subtype and molecular characteristics; subtypes include papillary, chromophobe, collecting duct, translocation, and unclassified.^{6,14} Due to their rarity, there are limited data to guide treatment for these tumors.¹² NCCN guidelines are listed in Table 2.

Systemic agents

Immunotherapies

ICIs that target the programmed cell death receptor 1 (PD-1) pathway, such as nivolumab, the programmed death-ligand 1 (PD-L1) pathway, such as avelumab, and/or the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) pathway, such as ipilimumab, have become the mainstay of therapy for aRCC.^{4,12}

Immunotherapy with high-dose IL-2 can promote tumor regression in some cases of aRCC, and although it can cause severe toxicity, responses often last for many years, and most complete responders do not relapse. While high-dose IL-2 was considered an important option for select patients

who tolerate it, its current role in the setting of more broadly effective and better tolerated ICIs is unclear; it could remain an option for favorable-risk disease, or for disease that has progressed after initial treatment with ICIs.^{12,13}

Molecularly targeted therapies

Antiangiogenic agents block the vascular endothelial growth factor (VEGF) pathway with either tyrosine kinase inhibitors (TKIs), such as sunitinib and cabozantinib, which block the intracellular domain of the VEGF receptor (VEGFR), or with bevacizumab, a monoclonal antibody, which binds VEGF and prevents it from activating the VEGFR.^{12,13,15}

The mTOR inhibitors everolimus and temsirolimus can impede tumor progression by inhibiting the mTOR pathway; however, single mTOR agents have a limited role in aRCC. They can be used for disease that is refractory to initial treatment with VEGFR TKIs and/or tumors that have mutations in the PI3K pathway, as well as for disease that has progressed on combination ICIs and cabozantinib.^{12,13,15}

Antiangiogenic agents plus ICIs

Combinations of ICIs plus antiangiogenic agents are effective in aRCC. Examples with overall survival (OS) benefit include pembrolizumab plus axitinib, cabozantinib plus nivolumab, and lenvatinib plus pembrolizumab.^{12,13}

Table 2. National Comprehensive Cancer Network treatment guidelines for clear cell and non-clear cell RCC

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	Preferred regimens	Other recommended regimens	Useful in certain circumstances
Favorable ^a	<ul style="list-style-type: none"> Axitinib + pembrolizumab^b Cabozantinib + nivolumab^b (category 1) Lenvatinib + pembrolizumab^b (category 1) 	<ul style="list-style-type: none"> Axitinib + avelumab^b Cabozantinib (category 2B) Ipilimumab + nivolumab^b Pazopanib Sunitinib 	<ul style="list-style-type: none"> Active surveillance^c Axitinib (category 2B) High-dose IL-2^d (category 2B)
Poor/intermediate ^a	<ul style="list-style-type: none"> Axitinib + pembrolizumab^b (category 1) Cabozantinib + nivolumab^b (category 1) Ipilimumab + nivolumab^b (category 1) Lenvatinib + pembrolizumab^b (category 1) Cabozantinib 	<ul style="list-style-type: none"> Axitinib + avelumab^b Pazopanib Sunitinib 	<ul style="list-style-type: none"> Axitinib^b (category 2B) High-dose IL-2^d (category 3) Temsirolimus^e (category 3)

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY			
Immuno-oncology (IO) Therapy History Status	Preferred regimens	Other recommended regimens	Useful in certain circumstances
IO Therapy Naïve	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Axitinib + pembrolizumab^b Cabozantinib Cabozantinib + nivolumab^b Ipilimumab + nivolumab^b Lenvatinib + everolimus Lenvatinib + pembrolizumab^b Nivolumab^b 	<ul style="list-style-type: none"> Axitinib Everolimus Pazopanib Sunitinib Tivozanib^f Belzutifan (category 2B) Bevacizumab^g (category 2B) High-dose IL-2 for selected patients^d (category 2B) Temsirolimus^e (category 2B) Axitinib + avelumab^b (category 3)
Prior IO Therapy	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Axitinib Cabozantinib Lenvatinib + everolimus Tivozanib^f 	<ul style="list-style-type: none"> Axitinib + pembrolizumab^b Cabozantinib + nivolumab^b Everolimus Ipilimumab + nivolumab^b Lenvatinib + pembrolizumab^b Pazopanib Sunitinib Belzutifan (category 2B) Bevacizumab^g (category 2B) High-dose IL-2 for selected patients^d (category 2B) Temsirolimus^e (category 2B) Axitinib + avelumab^b (category 3)

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY ^h		
Preferred regimens	Other recommended regimens	Useful in certain circumstances
<ul style="list-style-type: none"> Clinical trial Cabozantinib Sunitinib 	<ul style="list-style-type: none"> Lenvatinib + everolimus Nivolumab^b Nivolumab + cabozantinib Pembrolizumab^b 	<ul style="list-style-type: none"> Axitinib Bevacizumab^f Bevacizumab^f + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC) Bevacizumab^f + everolimus Erlotinib Everolimus Nivolumab + ipilimumab (category 2B) Pazopanib Temsirolimus^e (category 1 for poor-prognosis risk group; category 2A for other risk groups)

^a See Risk Models to Direct Treatment (IMDC criteria or MSKCC Prognostic Model) (KID-D).

^b See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

^c Rini BI, Doff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. *Lancet Oncol* 2016;17:1317-1324.

^d Patients with excellent performance status and normal organ function.

^e The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60-70, hemoglobin <LLN, corrected calcium >10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;356:2271-2281.

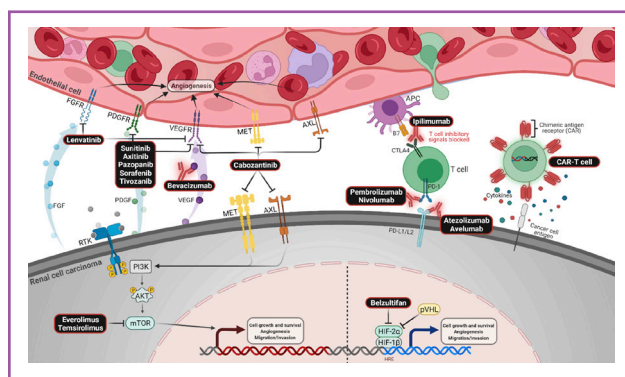
^f An FDA-approved biosimilar is an appropriate substitution for bevacizumab.

^g For patients who received ≥2 prior systemic therapies. Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Figure 1. Mechanisms of action of drugs for aRCC.



Reprinted with permission: Govindarajan A, Castro, DV, Zengin, et al. Front-Line Therapy for Metastatic Renal Cell Carcinoma: A Perspective on the Current Algorithm and Future Directions. *Cancers* 2022, 14, 2049. <https://doi.org/10.3390/cancers14092049>

Early loss of function of the von Hippel Lindau (*VHL*) gene during tumor growth in clear cell RCC causes hypoxia-inducible factor to accumulate, leading to excess proangiogenic factors, such as VEGF, fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF).¹⁶ Oral multitargeted TKIs, such as sunitinib, pazopanib, sorafenib, axitinib, and tivozanib, target this proangiogenic environment and destroy tumor cells by inhibiting downstream signaling of VEGF as well as other tyrosine kinases. Cabozantinib and lenvatinib target the VEGFRs and kinases, such as MET, AXL, and FGF receptor (FGFR). The selective monoclonal antibodies against VEGF also target angiogenesis and inhibit tumor growth by binding to VEGF⁶ (Fig. 1).

Cancer cells can activate the mTOR pathway through loss of p53, paracrine production of growth factors, mutations in the upstream components of PI3K, or mTOR complexes, such as TSC1/2, Lkb1, PTEN, and Nf1.^{17,18} Rapalogs decrease activation of the mTOR pathway by inhibiting the phosphorylation of mTOR and alter the translation of messenger RNA that codes for proteins involved in cell survival, proliferation, and angiogenesis¹⁷ (Fig. 1).

The PD-1/PD-L1 and the CTLA-4 checkpoints attenuate T-cell activation and are crucial in maintaining the balance between self-defense and self-tolerance.¹⁹ This balance can be dysregulated by tumor expression of checkpoint proteins, such as PD-L1, that promote immune tolerance of cancer cells. Blockers of PD-1/PD-L1 and CTLA-4 axes invigorate exhausted T cells to promote antitumor immunity²⁰ (Fig. 1).

Belzutifan inhibits the hypoxia-inducible factors (HIF-2 α -HIF-1B) interaction, leading to reduced expression of target genes related to cellular proliferation, angiogenesis, and tumor growth.¹²

Initial treatment options for clear cell aRCC

Due to results from several positive studies and its tolerability, the NCCN Kidney Cancer Panel lists sunitinib as a category 1 option for the first-line treatment of relapsed or stage IV clear cell RCC with favorable-, intermediate-, or poor-risk disease, and as a preferred therapy for relapsed or stage IV non-clear cell RCC. Therefore, multiple clinical trials have compared therapeutic options with sunitinib as the standard-of-care arm.^{12,21}

Nivolumab-ipilimumab for aRCC without prior systemic therapy improves OS compared with sunitinib²²⁻²⁴ and improves complete response (CR) rates across all patient subgroups.³ It is approved by the United States Food and Drug Administration (US FDA) for treatment-naïve patients with intermediate- or poor-risk aRCC. This combination is also used off-label as initial therapy for favorable-risk disease in patients who are symptomatic and/or have interval disease progression while on surveillance. In an open-label phase III trial (CheckMate 214), 1096 patients with treatment-naïve clear cell aRCC or metastatic RCC were randomly assigned to nivolumab plus ipilimumab versus sunitinib.^{22,23,25} At a median follow-up of 55 months, the combination, relative to sunitinib, demonstrated: improved OS (4-year OS of 53 vs 43%, hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.59-0.81); longer progression-free survival (PFS), although the results did not meet statistical significance (4-year PFS of 31 vs 17%, HR 0.89, 95% CI 0.76-1.05). Objective response rates (ORRs; 39 vs 32%) and CR rates (11 vs 3%) were also higher for the combination. Additionally, among those with a CR to the combination, 86% (51 of 59 patients) demonstrated ongoing disease response, and approximately half of those with durable responses (27 of 51 patients) discontinued therapy and did not require further treatment at long-term follow-up. Among those with a partial response (PR), 61% (95 of 156 patients) also demonstrated ongoing disease response.^{3,25}

Pembrolizumab-axitinib for aRCC without prior systemic therapy improves OS and PFS compared with sunitinib and is approved by the US FDA as initial therapy for patients with aRCC, for any risk classification. This combination has not been directly compared with other immunotherapy-based combinations. In a phase III trial (KEYNOTE-426), 861 patients with previously untreated clear cell aRCC were randomly assigned to pembrolizumab plus axitinib versus sunitinib alone. After a median follow-up of 31 months, relative to sunitinib, the combination improved OS (24-month OS of 74 vs 65%, HR 0.68, 95% CI 0.55-0.85), longer PFS (24-month PFS of 38 vs 27%, HR 0.71, 95% CI 0.60-0.84), higher ORRs (60 vs 40%), and higher CR rates (9 versus 3%).^{3,26,27}

Nivolumab-cabozantinib for aRCC without prior systemic therapy improves OS and PFS compared with sunitinib. This combination is approved by the US FDA as initial therapy for patients with aRCC, for any risk classification.²⁸ This combination has not been directly compared with other immunotherapy-based combination regimens. In a phase III trial (CheckMate 9ER), 651 patients with treatment-naïve aRCC were randomly assigned to either nivolumab plus cabozantinib or sunitinib. Patient subgroups included those with favorable-, intermediate-, or poor-risk disease. At median follow-up of 18 months, compared with sunitinib, the combination improved OS (1-year OS of 86 vs 76%, HR 0.60, 95% CI 0.40-0.89) and PFS (median 17 vs 8 months, HR 0.51, 95% CI 0.41-0.64). The combination also demonstrated higher ORRs (56 vs 27%) and CR rates (8 vs 5%). Median time to response was faster with the combination compared with sunitinib (2.8 vs 4.2 months).^{3,29}

Lenvatinib-pembrolizumab for treatment-naïve aRCC improved both OS and PFS in a randomized open-label phase III clinical trial (CLEAR),³⁰ in which 1069 patients with treatment-naïve aRCC were randomly assigned to either lenvatinib plus pembrolizumab; lenvatinib plus everolimus; or sunitinib. At median follow-up of approximately 27 months, relative to sunitinib, lenvatinib plus pembrolizumab had improved OS (medians not reached, HR 0.66, 95% CI 0.49-0.88) and longer PFS (median 24 vs 9 months, HR 0.39, 95% CI 0.32-0.49). ORRs were higher for the combination (71 vs 36%), including CR rates (16 vs 4%). In the randomized phase of the CLEAR trial, lenvatinib-everolimus improved PFS (median 15 vs 9 months, HR 0.65, 95% CI 0.53-0.80) over sunitinib, which was consistent across all IMDC subgroups. ORRs were also higher for the combination (54 vs 36%), including CR rates (10 vs 4%). However, OS was not higher for the combination (medians not reached, HR 1.15, 95% CI 0.88-1.50).^{3,30}

Avelumab-axitinib is an option for first-line therapy. In the phase III JAVELIN Renal 101 trial, 886 treatment-naïve patients with clear cell aRCC were randomly assigned to the combination versus sunitinib.^{31,32} At a median follow-up of approximately 19 months, compared with sunitinib, the combination demonstrated improved PFS (median 13.3 vs 8.0 months, HR 0.69, 95% CI 0.57-0.83) and higher ORRs (53 vs 27%). CR rates were similar for the two treatment arms (4 vs 2%). Although OS data are immature, the combination did not demonstrate an improvement in OS at data cutoff for the overall population (HR 0.80, 95% CI 0.62-1.03) or for any other patient subgroup.^{3,31,32}

Subsequent treatment options for clear cell aRCC

Patients who progress after initial immunotherapy and without prior antiangiogenic therapy can receive a VEGFR inhibitor. Options include axitinib, cabozantinib,³⁶ sunitinib, pazopanib, or lenvatinib with everolimus. Patients may also be offered nivolumab plus ipilimumab if they have no prior exposure to ipilimumab.³⁷ The addition of ipilimumab to nivolumab may “boost” response rates after progression on single-agent nivolumab, as was demonstrated in preliminary results from the TITAN-RCC (Tailored ImmunoTherapy Approach with Nivolumab in advanced Renal Cell Carcinoma) study.³⁸ Patients who progress after initial treatment with a VEGFR inhibitor plus immunotherapy combination can receive alternative targeted therapy.³

Patients who progress on initial treatment with a VEGFR inhibitor without previous exposure to ICIs, can receive nivolumab rather than further targeted therapy. Although data are limited, nivolumab plus ipilimumab may be an alternative option, based on phase I data from the CheckMate 016 trial and other observational data.^{37,39} Patients ineligible for immunotherapy may receive an alternative VEGFR inhibitor.³

Patients who progress on initial treatment with a VEGFR inhibitor without previous exposure to ICIs, may receive nivolumab, which improves OS, PFS, and ORR compared with everolimus in this population. In the phase III CheckMate

025 trial, 821 patients were randomly assigned to nivolumab or everolimus.⁴⁰⁻⁴⁴ All patients had received one or two prior antiangiogenic therapies. With a median follow-up of 64 months, relative to everolimus, single-agent nivolumab improved OS (median 25.8 vs 19.7 months, 5-year OS 26 vs 18%, HR 0.73, 95% CI 0.62-0.85); improved 5-year PFS (5 vs 1%, HR 0.84, 95% CI 0.72-0.99), although median PFS was similar between the two groups; higher ORR (23 vs 4%), including rare CR (1 vs 0.5%); and longer treatment-free interval among responders who came off treatment without subsequent systemic therapy (12.7 vs 4.1 months). Additional responses may be seen if nivolumab is continued after initial progression.⁴⁴ In the CheckMate 025 study, nivolumab therapy was also permitted after Response Evaluation Criteria in Solid Tumors (RECIST) progression if clinical benefit was observed.⁴³

Tivozanib, a multitargeted TKI, was recently added to the NCCN's other recommended subsequent monotherapy options for advanced ccRCC and is FDA-approved for adults who previously received two or more systemic therapies.^{12,45} Data from the randomized phase 3 multicenter TIVO-3 trial of tivozanib versus sorafenib in patients with relapsed or refractory advanced ccRCC, supported the drug's approval. Patients receiving tivozanib had significantly longer PFS than those receiving sorafenib and OS was similar between the two groups.⁴⁶ Median PFS was 5.6 months (95% CI: 4.8, 7.3) in the tivozanib arm (n=175) compared with 3.9 months (95% CI: 3.7, 5.6) for those treated with sorafenib (HR 0.73; 95% CI: 0.56, 0.95; p=0.016). Median OS was 16.4 (95% CI: 13.4, 21.9) and 19.2 months (95% CI: 14.9, 24.2), for the tivozanib and sorafenib arms, respectively (HR 0.97; 95% CI: 0.75, 1.24). The ORR was 18% (95% CI: 12%, 24%) for the tivozanib arm and 8% (95% CI: 4%, 13%) for the sorafenib arm.^{45,46} A recent analysis also demonstrated that tivozanib also increased quality-adjusted time without symptoms of disease and toxicity (Q-TWiST) as compared to sorafenib (15.04 months vs. 12.78 months, respectively).^{12,47}

Treatment options for non-clear cell aRCC

Clinical trials of targeted agents have focused primarily on clear cell rather than non-clear cell histology due to its much higher prevalence than non-clear cell subtypes.^{12,48} Because the role of targeted agents in non-clear cell RCC warrants investigation, the NCCN Panel recommends enrollment in clinical trials as the preferred strategy for non-clear cell RCC.¹²

There are data indicating that targeted therapies approved for clear cell RCC may have benefit for non-clear cell RCC, including randomized phase II trials, systematic reviews, meta-analysis of phase II studies, and retrospective studies with targeted agents. Compared with responses in clear cell histologies, however, the response rates with these agents are significantly lower for non-clear cell RCC.¹² Specific recommendations for non-clear cell aRCC are listed in Table 2.

Systemic therapy and the kidneys

In early-stage RCC, developing chronic kidney disease (CKD) may be related to pre-existing kidney damage and/or nephrectomy-related nephron loss. In aRCC, however, CKD may arise from hypertension, proteinuria, nephrotoxicity, and other side effects caused by systemic therapies. Anti-angiogenic drugs often cause hypertension, and less frequently proteinuria, including within the nephrotic range. A variety of agents are used to treat hypertension and proteinuria, including renin angiotensin system inhibitors and calcium channel blockers, but there are no randomized clinical trials comparing different therapeutic agents in these patients.⁴⁹

ICIs are also associated with a host of side effects that affect almost every organ in a manner that resembles autoimmune disease. In the kidney, these drugs can induce acute interstitial nephritis in close to 5% of patients, and in some

cases require discontinuing treatment, along with receiving systemic corticosteroids. Moreover, all clinical trials involving mTOR inhibitors have been performed in patients with normal kidney function; therefore, their effects in patients with kidney dysfunction are unknown.⁴⁹

Considering the potential for treatment-related kidney damage, kidney function must be assessed regularly before, during, and after systemic therapy. Interdisciplinary care involving the oncologist and nephrologist, as well as a pathologist, who can determine if there is any underlying premetastatic disease prior to treatment, is optimal. This approach is especially important in an aging population that may have other risk factors for CKD, such as hypertension and diabetes, and/or a history of nephrectomy.⁵⁰

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