

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of renal cell carcinoma, version 3.0

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ABSTRACT

Immunotherapy has been a pillar of the renal cell carcinoma (RCC) treatment landscape for over three decades. Some of the earliest cancer immunotherapies available, such as interleukin 2 and interferon-alpha, have resulted in complete responses, but only in a small number of patients. Immune checkpoint inhibitors (ICIs), however, have demonstrated improved response rates and prolonged survival for a greater number of patients, fully transforming the standard of care in first-line and subsequent-line settings. More recently, ICIs are also being used in the adjuvant setting for high-risk patients. However, treatment with ICIs requires a nuanced understanding of topics such as patient selection, histology and risk considerations, and integration with local therapies. As such, the Society for Immunotherapy of Cancer (SITC) convened a panel of experts to develop this clinical practice guideline (CPG) on immunotherapy for the treatment of RCC. Drawing from published data and clinical experience, the Expert Panel developed evidence-based and consensus-based recommendations. Topics include therapy selection in the adjuvant and metastatic settings, considerations for special patient populations, response monitoring, and patient education and quality of life considerations, among others, with the goal of improving patient care by providing guidance to the oncology community.

INTRODUCTION

Kidney cancer accounts for 4%–5% of all cancers diagnosed in the USA,¹ with an increasing incidence.² Fortunately, mortality rates have steadily declined 1%–2% annually.² While much of the improved survival outcomes over the past 50 years are related to incidental identification of small renal masses, advances in treatment regimens may have contributed, with immunotherapy currently at the forefront of this dynamic treatment landscape.

Renal cell carcinoma (RCC) is a subset of kidney cancer that is typically not responsive to chemotherapy,³ and therefore, treatment modalities include surgical intervention, local radiation, targeted agents, and immunotherapy. RCC is a highly immune-infiltrated tumor, enabling immunotherapy approaches to reactivate suppressed antitumor immune responses.⁴ In fact, some of the earliest approved immunotherapies, interleukin 2 (IL-2) and interferon-alpha (IFN-alpha), were long the standard of care (SOC) and often the only therapeutic options for patients with metastatic RCC before 2004.^{5,6} Response rates to these early immunotherapies were modest, however, often limited to 5%–20% of patients.^{5,6} The use of angiogenesis-targeting agents, such as vascular endothelial growth factor receptor (VEGFR)-directed tyrosine kinase inhibitors (TKIs), has demonstrated improved clinical benefit for many patients with advanced/metastatic RCC.⁷ However, developing resistance and absence of treatment alternatives have limited the benefit of these approaches.^{8,9} With the continued investigation of immunotherapy approaches in the last two decades, immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1), its ligand (PD-L1), and cytotoxic T lymphocyte antigen-4 (CTLA-4) are now SOC treatments in first-line and subsequent-line settings in RCC. Additionally, adjuvant ICI therapy is being incorporated for treatment of localized disease for selected patients. ICIs, either as single agents or in combination with other ICIs or anti-angiogenic targeted agents, have provided higher response rates, more durable responses and improved survival



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outcomes for patients with RCC compared with VEGFR TKI monotherapy.^{10–13}

While the success of ICIs has improved outcomes for many patients, a number of challenging clinical questions remain. Biomarkers indicative of immunogenicity (eg, tumor mutational burden [TMB], PD-L1 expression, and mismatch repair [MMR]/microsatellite instability [MSI] status) have not been shown to be clinically useful in guiding patient selection for ICI treatment for RCC.¹⁴ Additionally, the risk stratification models (eg, The International Metastatic RCC Database Consortium [IMDC], Memorial Sloan-Kettering Cancer Center [MSKCC]) developed for prognostication with VEGFR TKIs have been integrated into clinical trials of ICIs, though have limited utility in treatment selection.^{15–19} Moreover, choosing an appropriate immunotherapy-based treatment remains challenging, as there is no head-to-head data comparing the several Food and Drug Administration (FDA)-approved immunotherapies for metastatic disease. As both systemic and local therapies continue to develop, the integration and sequencing of immunotherapy with local therapies for ICI-resistant or ICI-refractory disease has also become increasingly complicated. Other important clinical considerations include the management of special patient populations, ICI treatment duration and response monitoring, patient and caregiver education, and quality of life (QOL) concerns. For the purpose of this guideline, all mentions of RCC will be specific to clear-cell RCC (ccRCC) unless specifically noted.

To address these clinical challenges, the Society for Immunotherapy of Cancer (SITC) convened a multidisciplinary panel of experts to develop this clinical practice guideline (CPG). This serves as an update from the previous CPG for treatment of RCC published in 2019 and focuses on improving patient care by providing evidence-based and consensus-based recommendations for the treatment of RCC using immunotherapy approaches. SITC CPGs are developed to assist providers in clinical decision-making and do not mandate a particular course of treatment or medical care. The CPGs are not intended to supplant sound judgment by the treating physician with respect to individual patients or special clinical situations and cannot always account for variation among patients. SITC considers adherence to the guidance to be voluntary, with the ultimate determination for the selected course of action to be made by the physician in light of each patient's individual circumstances.

GUIDELINE DEVELOPMENT METHODS

This CPG was developed by the SITC Renal Cell Carcinoma Immunotherapy Guideline Expert Panel, under the governance of the SITC Cancer Immunotherapy Guidelines Oversight Committee. The Institute of Medicine's (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines were used as a model for guideline development.

Expert Panel composition

The guideline development group was multidisciplinary and balanced. Members were selected based on their expertise and experience in the field, including medical oncology, nursing, and patient advocacy, as well as other specialties as needed to support recommendation development.

Conflict of interest management

Disclosures of all financial relationships that might result in actual, potential, or perceived conflicts of interest were individually reported prior to the onset of manuscript development as well as at all key decision points during manuscript development. Those with significant financial connections that may compromise the ability to fairly weigh evidence (either actual or perceived) were not eligible to participate in guideline development. Any non-disqualifying conflicts of interest among members of the SITC Renal Cell Carcinoma Immunotherapy Guideline Expert Panel were managed as outlined in SITC's disclosure and conflict of interest resolution policies.

The financial support for the development of this guideline was provided solely by SITC. No commercial funding was received.

Recommendation development

Panel recommendations are based on literature evidence, where possible, and clinical experience, where appropriate. Literature searches in relevant databases were performed, and publications were screened for inclusion in the evidence base for the guideline recommendations. Recommendations were developed based both on literature review and expert opinion presented during open communication and scientific debate. Subsequently, recommendations were refined through a modified Delphi process as described by the RAND/University of California, Los Angeles (UCLA) Appropriateness Method, Expert Panel consensus discussions, and review and editing of manuscript drafts. For inclusion in SITC's CPGs, all recommendations have reached at least 85% consensus among the Expert Panel. The strength of the recommendations included in this CPG is approximate to National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines) Category 1 or Category 2A. This may be useful for third-party payor reimbursement. Additional information is discussed in the narrative text to provide further context, detail, and/or nuance that is clinically relevant for health-care providers using these therapies.

Evidence rating

The level of evidence (LE) for a given consensus recommendation is expressed in parentheses following the recommendation (eg, LE:1). Evidence supporting panel recommendations was graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence Working Group "The Oxford Levels of Evidence 2", summarized below. Recommendations without an

associated LE are based on Expert Panel consensus or are standard clinical practice.

- ▶ **Level 1:** Systematic review of randomized controlled trials.
- ▶ **Level 2:** Randomized controlled trial or observational study with dramatic effect.
- ▶ **Level 3:** Non-randomized controlled cohort or follow-up study.
- ▶ **Level 4:** Case series, case-control, or historically controlled study.
- ▶ **Level 5:** Mechanism-based reasoning.

External review

A draft of this CPG was made publicly available to provide an opportunity for stakeholders potentially affected by guidelines to review and comment on the content. All comments were evaluated by the Expert Panel and considered for inclusion into the final manuscript.

DIAGNOSTIC TESTS AND BIOMARKERS

General diagnostic tests and staging

The staging and risk stratification of RCC is critical in determining eligibility for systemic therapies, including immunotherapies.^{20 21} The diagnostic workup for renal masses typically includes initial radiographic imaging, often contrast-enhanced CT or MRI,²² and confirmation via pathology is often recommended (especially for small renal masses and unresectable tumors). Additional diagnostic tests may include blood work (eg, complete blood count [CBC], and metabolic panel). Additional imaging modalities, such as positron emission tomography (PET)/CT, are under investigation for future applicability in RCC diagnostics.^{23–26} For patients with isolated renal masses, a partial or complete nephrectomy can provide tissue for diagnosis and serve as definitive treatment. Conversely, for patients with suspected metastatic disease, additional imaging²² and a biopsy of a metastatic site are typically necessary.²⁷ RCC tumors are staged using the American Joint Committee on Cancer (AJCC) 8th Edition Tumor, Node, Metastasis (TNM) staging system,²¹ and additional aspects of risk stratification include histologic grade, subtype determinations, and sarcomatoid or rhabdoid dedifferentiation features (see **Histology** section) and vary by presence or absence of metastases.²⁸

IMDC classification

IMDC classification is a comprehensive scoring system that uses clinical-based and laboratory-based parameters to predict clinical outcomes for patients with stage IV/metastatic RCC treated with systemic therapy.^{17 18} The IMDC classification was originally designed as a prognostic tool that was validated when VEGFR TKIs were the SOC for metastatic disease and has been useful for patient stratification in clinical trials. While it has been integrated into clinical trials of immunotherapy and remains prognostic in the modern era, its role in informing immunotherapy treatment decisions is limited.

Histology

The histological subtypes of RCC are distinct biologic entities with unique pathogenesis and immunologic profiles, and therefore have both prognostic and therapeutic implications. The main RCC histology is ccRCC, accounting for 75% of all RCC cases.²⁸ Papillary and chromophobe are the most common non-ccRCC (nccRCC) histological subtypes, making up 90% of cases, while the remainder are rare subtypes.²⁸ At the time of guideline publication, there were no approved immunotherapies specifically for nccRCC. Importantly, while there have been a small number of trials or small studies (see **Adjuvant immune checkpoint inhibition – non-clear cell RCC** and **Available immunotherapy for nccRCC** sections) assessing ICIs for treatment of nccRCC,^{29–36} most treatment recommendations have been extrapolated from ccRCC studies.^{37 38} As such, much of the text within this guideline refers to ccRCC, and any references to nccRCC data will be specified. The newest edition of the WHO classification of urogenital tumors published in 2022 includes classifications based on molecular subtypes of renal tumors^{39–41}; however, the clinical utility of the molecular classifications, especially as it relates to immunotherapy treatment decisions, is uncertain at the time of guideline publication.

Histologic grade

In addition to characterizing tumor type, it is important to determine tumor grade, which is an independent factor in prognosis. The original grading system for RCC was Fuhrman grade, which was based on nuclear size, shape/irregularity, and nucleolar prominence.⁴² In 2017 the WHO implemented a tumor classification system that included a grading system developed by the International Society of Urologic Pathologists (ISUP).⁴³ This WHO/ISUP grading system was based on nuclear morphology assessment of tumors for ccRCC and papillary RCC^{44 45} and demonstrated improved prognostic indications compared with the Fuhrman grading system. Within this grading system, grade 4 tumors are defined as having extreme nuclear pleomorphism with rhabdoid and/or sarcomatoid morphology.

While infrequent, rhabdoid and/or sarcomatoid dedifferentiations can occur in any histological subtype and are associated with poor prognoses. These features may also impact responses to ICIs.⁴⁶ Sarcomatoid features are associated with strong responses to ICIs, as demonstrated in a subgroup analysis in CheckMate 214 (NCT02231749). At 42 months minimum follow-up, patients with sarcomatoid features experienced markedly improved overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) with ipilimumab (an anti-CTLA4 antibody) plus nivolumab (an anti-PD-1 antibody) versus sunitinib (see the **Stage II, stage III, and stage IV RCC amenable to metastasis-directed therapy** section for more details from the study).⁴⁷ There are limited data related to ICI efficacy in patients with rhabdoid features; however, they should not be excluded from ICI-based regimens.

Immunotherapy-specific biomarkers

While some biomarkers predictive of response to ICIs have demonstrated clinical significance across many types of solid tumors, their utility in RCC is limited. These include high TMB (TMB-H), high MSI (MSI-H), MMR deficiency (dMMR), and PD-L1 expression,^{48 49} which are the basis of both tissue-agnostic and disease-specific ICI indications.^{50–52}

In RCC, landmark trials such as JAVELIN Renal 101, Immotion151, and KEYNOTE-426 found that while responses were often slightly higher for PD-L1-positive tumors, patients with PD-L1-negative tumors also responded and therefore the differences compared with the overall/intent-to-treat (ITT) populations were not significant.^{10 53–56} TMB is relatively low in RCC, with a median TMB of <5 mutations/megabase (mut/Mb) in various studies, though there are rare instances of TMBs over 400 mut/Mb.^{57–60} Moreover, while pembrolizumab is approved for use in recurrent, unresectable, or metastatic TMB-H solid tumors, no patients with RCC were included in KEYNOTE-158, which was the trial assessed for this approval.^{61 62} Similarly, while MSI-H and dMMR are also biomarkers used in tissue-agnostic ICI approvals,^{62 63} they are also rare in RCC. One analysis of The Cancer Genome Atlas (TCGA) and Therapeutically Applicable Research to Generate Effective Treatments (TARGET) data showed that less than 2% of RCC tumors (clear cell, papillary, and chromophobe) were MSI-H.^{64 65} Another study (n=753) showed only 4% of RCC tumors were dMMR.⁶⁰ Kidney injury molecule-1 (KIM-1) is a transmembrane protein that is overexpressed in RCC and shed into the blood. High KIM-1 after nephrectomy is associated with benefit from adjuvant immunotherapy, and a decrease in KIM-1 after treatment is associated with response to immunotherapy.^{66–68} Further studies on KIM-1 are ongoing and may ultimately provide a basis for clinical use of this biomarker in the future.

Taken together, these markers are not currently clinically useful in driving treatment decisions for patients with RCC.⁶⁹ Additionally, there is a limited role for PET imaging and circulating tumor DNA (ctDNA) assessment for monitoring responses to ICIs in patients with RCC.^{70–72} However, the most clinically applicable predictive biomarker for use of ICI treatment in RCC is the presence of sarcomatoid differentiation (see **Histologic grade** section).

Expert Panel recommendations

- ▶ For patients with suspected RCC, pathology should confirm the diagnosis (LE:3).
- ▶ For patients with sarcomatoid (LE:1)/rhabdoid (LE:4) differentiation/features, patients may have improved outcomes to immunotherapy and should be considered for immune-based regimens.
- ▶ For patients with RCC, TMB (LE:2), MSI/MMR status, PD-L1 expression (LE:3), and/or specific genetic mutations (eg, *PBRM1*) are not recommended for patient selection for immunotherapy.

STAGE II, STAGE III, AND STAGE IV RCC AMENABLE TO METASTASIS-DIRECTED THERAPY

Localized disease accounts for approximately two-thirds of all RCC cases⁷³ and has an excellent survival prognosis with the 5-year relative survival rate of approximately 93% for localized disease and 70% for regional disease.^{2 74} Before the approval of adjuvant pembrolizumab, there were a number of efforts to find adjuvant therapies for patients at high risk of relapse after resection, including IFN-alpha, IL-2, and VEGFR TKIs.⁷⁴ Ultimately, most showed no benefit over observation and came with significant toxicity. Though several VEGFR TKIs had negative results in large landmark trials, sunitinib is approved for adjuvant treatment of RCC based on a small improvement in disease-free survival (DFS) over placebo.^{75 76} However, follow-up studies found no OS benefit.^{74 75 77} Currently, pembrolizumab is approved for the adjuvant treatment of high-risk resected RCC. Details of this approval are described in the **Adjuvant immune checkpoint inhibition** section below, and the overall treatment strategy for patients with resectable RCC (ccRCC and nccRCC) is provided as a treatment algorithm in [figure 1](#).

Imaging and risk assessment

Patients with RCC should undergo cross-sectional imaging (abdominal CT or MRI)⁷⁸ no more than 3 months before beginning adjuvant therapy. Depending on the timing of initial imaging, prior treatments, and surgery, new imaging may be required.

For patients with localized RCC who undergo either partial or radical nephrectomy, approximately 20%–40% will experience disease recurrence.^{79–81} As such, not all patients will benefit from adjuvant systemic therapy over surveillance. Due to the increased risk for toxicity with systemic therapies, careful risk/benefit assessments and discussions with patients are important. Several risk assessment nomograms/models serve to predict prognosis and risk of disease recurrence based on stage, grade and other pathologic and clinical parameters, including models from Mayo Clinic⁸² and MSKCC,⁸³ European association of urology renal cell carcinoma guidelines panel collaborative multicenter consortium for the studies of follow-up and recurrence patterns in radically treated renal cell carcinoma patients (RECUR),^{84–87} ASSURE,^{81 88} University of California Los Angeles Ingerated Staging System (UISS),⁸⁹ Leibovich⁹⁰ and others.^{81 88} Of note, KEYNOTE-564 used an adapted risk model based on existing nomograms, TNM, and Fuhrman grading status to assess grade and stage and to assign risk.

Adjuvant immune checkpoint inhibition

Clear-cell RCC

Pembrolizumab was approved on November 17, 2021, for patients with RCC with intermediate-to-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions⁹¹ based on data from the double-blinded, phase III trial KEYNOTE-564 (NCT03142334).⁹² The intermediate-to-high risk

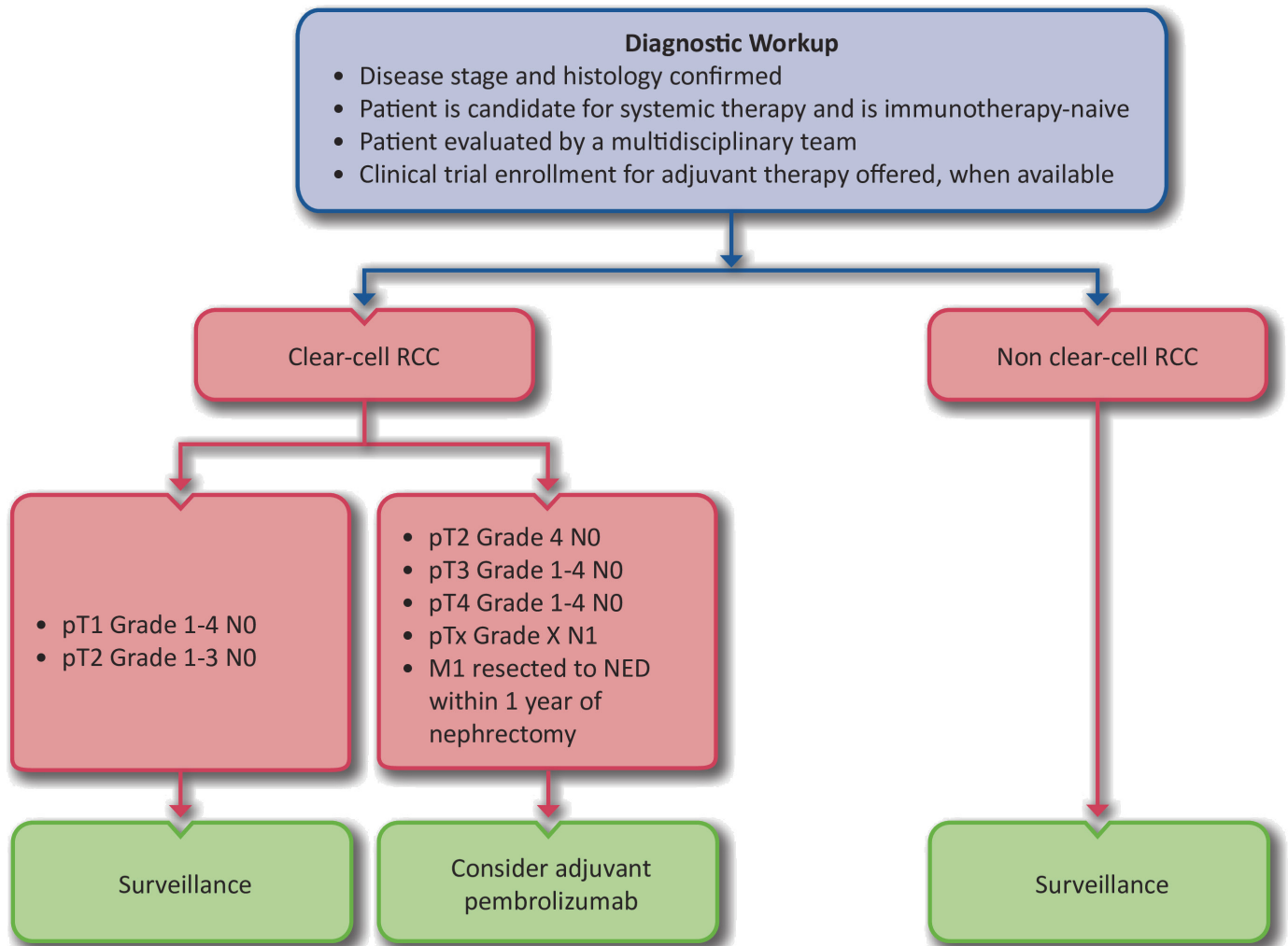


Figure 1 Adjuvant immunotherapy treatment algorithm for patients with RCC.
NED, no evidence of disease; RCC, renal cell carcinoma.

category included patients with pT2, grade 4 or sarcomatoid features, N0, M0; or pT3, any grade, N0, M0. The high-risk category included patients with pT4, any grade, N0, M0; or pT any stage, any grade, nodal involvement (N+), M0. The M1 no evidence of disease (NED) category included patients who presented with a primary kidney tumor with metastases that were completely resected at the time of or ≤ 1 year from nephrectomy. At the first prespecified interim analysis (median time from randomization to the data cutoff 24.1 months), the primary endpoint of DFS was significantly improved compared with placebo (HR 0.68; 95% CI 0.53 to 0.87; $p=0.002$), leading to the approval, which was maintained at the 30-month follow-up (HR 0.63; 95% CI 0.50 to 0.80; [table 1](#)).⁹³ At a third interim analysis (median follow-up 57.2 months), a significant improvement in OS was also demonstrated (HR 0.62; 95% CI 0.44 to 0.87; $p=0.005$).⁹⁴ While median OS (mOS) was not reached (NR), the estimated OS rates for adjuvant pembrolizumab versus placebo at 48 months were 91.2% and 86.0%, respectively. Additionally, the observed DFS benefit with pembrolizumab versus placebo was maintained ([table 1](#)). In the pembrolizumab

group, the estimated rate of patients alive without recurrence at 48 months was 64.9% (95% CI 60.3% to 69.1%) compared with 56.6% (95% CI 52.0% to 60.9%) for placebo. In subgroup analyses of the various recurrence risk groups (M0 intermediate-high risk, M0 high risk, M1 NED), OS and DFS both favored pembrolizumab in all groups; however, the DFS benefit was stronger compared with placebo in the higher-risk groups.

Patients in the KEYNOTE-564 had not received prior systemic therapy for RCC and were treated on the study for approximately 1 year. Three-week interval dosing (200 milligram [mg] intravenously) of pembrolizumab was used in the study;⁹² however, 6-week interval dosing (400 mg intravenously) is also available.³⁶ For patients undergoing adjuvant pembrolizumab treatment, cross-sectional imaging (chest CT and CT/MRI of abdomen; approximately every 3 months) and laboratory studies (complete metabolic panel [CMP], CBC, thyroid stimulating hormone [TSH]) should be obtained periodically for the duration of treatment.

Despite the validated benefit of adjuvant pembrolizumab observed in KEYNOTE-564, other phase III trials

Table 1 Landmark ICI trial data for adjuvant treatment of RCC

Trial and data analysis information	Agent(s) investigated	Study population	Primary end point
KEYNOTE-564 (NCT03142334) ⁶²	Pembrolizumab (200 mg)	Patients with resected ccRCC who had not previously received systemic therapy with intermediate–high or high risk of recurrence, or M1 NED	Median DFS (reported at 30-month analysis): NR (95% CI NR to NR)
Median f/u (DFS HR) 57.2 months	n=496		HR 0.72 (95% CI 0.59 to 0.87)
	Placebo		Median DFS (reported at 30-month analysis): NR (95% CI 40.5 months to NR)
Median f/u (median DFS) 30.1 months ^{93 94}	n=498		
ccRCC, clear-cell RCC; DFS, disease-free survival; f/u, follow-up; ICI, immune checkpoint inhibitor; mg, milligram; NED, no evidence of disease; NR, not reached; RCC, renal cell carcinoma.			

assessing ICIs in this setting have not shown consistent clinical benefit for adjuvant ICI treatment of resected ccRCC with increased risk of relapse. In CheckMate 914 (NCT03138512), which assessed the efficacy of adjuvant nivolumab plus ipilimumab versus placebo, at a median follow-up of 37 months the dual ICI therapy did not improve DFS.⁹⁵ Part B of CheckMate 914, which evaluated nivolumab monotherapy versus placebo, also did not show an improvement in DFS with nivolumab at a median follow-up of 27 months.⁹⁶ Similarly, IMmotion010 (NCT03024996) analyzed adjuvant atezolizumab in a multicenter randomized trial. Median DFS for atezolizumab (57.2 months; 95% CI 44.6 to not evaluable [NE]) was not significantly improved compared with placebo (49.5 months [95% CI 47.4 to NE]; HR 0.93 [95% CI 0.75 to 1.15; $p=0.50$]).³⁰ The PROSPER trial (NCT03055013) assessed a perioperative ICI regimen where nivolumab was given before and after surgery compared with nephrectomy alone; however, the trial was stopped early due to futility, and at the time of study termination, recurrence-free survival was similar between the treatment arms.⁹⁷ The exact reason for the inconsistent data around adjuvant ICIs is unknown, though some potential explanations include differences in agent mechanism of action, trial design, population risk, and dose exposure.^{98 99} Nevertheless, the mixed data in this setting should be taken into consideration in the risk/benefit discussion with patients. There are a few alternatives to adjuvant pembrolizumab treatment. For patients who prefer, surveillance is a reasonable option given the immune-related adverse events (irAEs) risk with ICIs, the existing negative data for other adjuvant ICIs, and the high percentage of patients in KEYNOTE-564 who had not yet experienced disease recurrence or death in the placebo group, even up to 48 months after treatment.^{92 98} Additionally, the DFS benefit of adjuvant pembrolizumab varied depending on the subgroup and was lower for those with lower risk of recurrence, and therefore, adjuvant pembrolizumab may be less clinically useful in these settings. Lastly,

while adjuvant sunitinib should not be used routinely, for patients with contraindications to ICIs, sunitinib is an option.^{75 100}

Serious adverse events (AEs) attributed to the study treatment occurred in 12% of patients in the pembrolizumab treatment group and <1% in the placebo group.⁹³ The rate of high-dose systemic corticosteroid administration for the treatment of irAEs was 8% for the pembrolizumab group and 1% in the placebo group. Consistent with previous reports, at median follow-up of 57.2 months pembrolizumab was associated with a higher incidence of grade 3 or 4 AEs (18.6%) compared with placebo (1.2%).⁹⁴ A total of 10 serious treatment-related AEs (TRAEs) occurred in the pembrolizumab group beyond 90 days of treatment cessation. The incidence of immune-mediated AEs was 36.5% with pembrolizumab versus 7.3% with placebo. No deaths were attributed to pembrolizumab therapy.

Some patients will experience disease recurrence after receiving adjuvant pembrolizumab.⁹⁴ Unfortunately, at the time of guideline publication, there are limited prospective data to inform subsequent treatment options for these patients, and most evidence for systemic or local treatment options is extrapolated from patients with metastatic RCC treated with ICIs. Local therapies such as metastasectomy¹⁰¹ or radiotherapy¹⁰² may be used for limited recurrence (see **RCC-specific considerations for ICI treatment – Oligoprogressive and oligometastatic disease** section for more information), and clinical trial enrollment is encouraged.

Non-clear cell RCC

In comparison to ccRCC, nccRCC is understudied, and currently, there are no approved adjuvant immunotherapies for nccRCC histologies. Moreover, the clinical benefit demonstrated in KEYNOTE-564 for ccRCC cannot be extrapolated to nccRCC. Some studies have assessed or are in the process of assessing neoadjuvant or adjuvant ICIs for resectable nccRCC, including the PROSPER (assessing preoperative

nivolumab followed by adjuvant nivolumab vs surgery only)²⁹ and IMmotion010 (assessing adjuvant atezolizumab vs placebo)³⁰ trials which included patients with nccRCC. Although the number of patients with nccRCC included in these studies was small (n=139 for PROSPER; n=58 for IMmotion010), neither trial showed clinical benefit for ICIs in the overall populations. Additional post hoc analyses within the PROSPER trial on patients with chromophobe and papillary histologies showed no benefit for perioperative nivolumab. The RAMPART trial (NCT03288532), assessing adjuvant durvalumab with and without tremelimumab, also has planned subgroup analyses for patients with nccRCC; however, these data have not yet been reported. Given the lack of data and treatment options for patients with resected nccRCC with increased risk of recurrence, clinical trial enrollment is highly encouraged.

Emerging immunotherapy strategies for resectable RCC

At the time of publication, there are several additional studies that are investigating perioperative immunotherapies for resected RCC. As stated above, the phase III RAMPART trial is ongoing with an estimated completion date of 2034. Additionally, the ongoing phase III LITESPARK-022 trial (NCT05239728) is comparing adjuvant pembrolizumab versus pembrolizumab with the hypoxia-inducible factor-2 alpha (HIF-2 α) inhibitor belzutifan in patients with ccRCC.¹⁰³ Neoadjuvant immunotherapy for patients with non-metastatic RCC that is unresectable (due to size or bilateral tumors, inferior vena caval thrombus, postoperative morbidity, etc) is also an active area of investigation; however, no studies to date have shown significant efficacy.¹⁰⁴

Important factors when considering neoadjuvant therapy include optimal timing with surgery and potential irAEs that may complicate or delay surgery. Clinical trial enrollment in neoadjuvant studies is encouraged to understand the benefit of immune modulation before surgery. Finally, other immunomodulating strategies that are under investigation in earlier phases of study include messenger RNA,¹⁰⁵ neo-antigen,^{106 107} and dendritic cell vaccines,¹⁰⁸ and microbiome modulation.¹⁰⁹ Within ongoing clinical trials, investigators are also looking for predictive/prognostic biomarkers that may help stratify patients into treatment groups.

Expert Panel recommendations

- Use of validated nomograms (eg, ASSURE, Mayo Clinic, UISS) may be useful to further guide consideration for use of adjuvant pembrolizumab for patients who are eligible (LE:3–LE:4).
- For patients with resected RCC, clinical trial enrollment for adjuvant therapy should be offered when available.

- For patients with resected RCC who are eligible, discussion of treatment risks and benefits of adjuvant ICI therapy is recommended.
- For patients with resected RCC who have pT2 with Fuhrman grade 4 or sarcomatoid differentiation, pT3 or higher, regional lymph node metastasis, or M1 NED, adjuvant pembrolizumab should be considered (LE:1).
- For patients with resected RCC who are starting adjuvant systemic therapy, imaging should be obtained within 3 months prior to initiation.
- For patients with resected RCC who will be receiving adjuvant pembrolizumab, treatment should be initiated within 3–4 months of surgery and should be continued for 1 year.
- For patients with resected RCC who experience disease progression during or within 1 year after receiving adjuvant pembrolizumab, there is currently no level one evidence to guide standard treatment.
- For patients with resected RCC who experience disease progression during or within 1 year after receiving adjuvant pembrolizumab, although the data are limited, metastasectomy, ablation, or radiotherapy may be considered for limited recurrence (LE:3).
- For patients with resected nccRCC, there is no SOC adjuvant therapy, and clinical trial enrollment is recommended, when available and appropriate.
- There is no standard neoadjuvant regimen for patients with non-metastatic localized RCC, and a multidisciplinary consultation should be considered to determine the best management strategy for these patients.

STAGE IV RCC

Stage IV disease is less common than localized disease, with unresectable disease comprising about one-third of RCC diagnoses.⁷³ Before the development of immunotherapies beyond IL-2 and IFN-alpha, patients with advanced disease had limited options for systemic therapy and a 5-year survival rate of less than 10%.¹¹⁰ In the interim, targeted therapy with VEGFR TKIs became a standard treatment approach, which improved outcomes compared with placebo and had less toxicity compared with cytokine treatments,^{111 112} although response durability was low. The advancements of ICIs demonstrated significant improvements in response rates and survival, and as a result, they became the new SOC.¹¹³ At the time of guideline publication, three ICI plus VEGFR TKI combination therapies and one dual ICI therapy are FDA-approved for first-line treatment of advanced ccRCC. For the landmark trials and data that led to the FDA approvals of these combinations, see [table 2](#) and the **Available immunotherapy for treatment-naïve ccRCC** section.

Table 2 Landmark ICI trials and data for first-line treatment of stage IV ccRCC

Trial and data analysis information	Agent(s) investigated	Study endpoints		
		Median PFS*	ORR	Median OS*
KEYNOTE-426 (NCT02853331) Phase III Randomized Median f/u 43 months ¹²⁶	Pembrolizumab (200 mg) + axitinib (5 mg) n=432	16 months (95% CI 14 to 20) HR 0.68 (95% CI 0.58 to 0.80)	60% (95% CI 56% to 65%)	46 months HR 0.73 (95% CI 0.60 to 0.88)
	Sunitinib (control; 50 mg)	11 months (95% CI 8.9 to 13)	40% (95% CI 35% to 44%)	40 months
	n=429			
		Median PFS*	ORR	Median OS
CheckMate 9ER (NCT03141177) Phase III Randomized Median f/u 44.0 months ¹²⁹	Nivolumab (240 mg) + cabozantinib (40 mg) n=323	16.6 months (95% CI 12.8 to 19.5) HR 0.59 (95% CI 0.49 to 0.71)	56% (95% CI 50% to 62%)	49.5 months (95% CI 40.3 to NE) HR 0.70 (95% CI 0.56 to 0.87)
	Sunitinib (control; 50 mg)	8.4 months (95% CI 7 to 9.7)	28% (95% CI 23% to 33%)	35.5 months (95% CI 29.2 to 42.3)
	n=328			
		Median PFS*	ORR	Median OS
CLEAR (Study 307/KEYNOTE-581) (NCT02811861) Phase III Randomized PFS median f/u 39.2 months pembrolizumab+lenvatinib group and 20.6 months in sunitinib group ¹³⁴ OS median f/u 49.8 months in pembrolizumab+lenvatinib group and 49.4 months in sunitinib group ⁹⁶	Pembrolizumab (200 mg) + lenvatinib (20 mg) n=355	23.9 months (95% CI 20.8 to 27.7) HR 0.47 (95% CI 0.38 to 0.57; p<0.0001)	71.3% (95% CI 66.6% to 76.0%)	53.7 months (95% CI 48.7 to NE) HR 0.79 (95% CI 0.63 to 0.99; p=0.0424)
	Sunitinib (control; 50 mg)	9.2 months (95% CI 6.0 to 11.0)	36.7% (95% CI 31.7% to 41.7%)	54.3 months (95% CI 40.9 to NE)
	n=357			
		Median PFS*	ORR*	Median OS*
CheckMate 214 (NCT02231749) Phase III Randomized Median f/u 9 years ²⁴⁸	Nivolumab (3 mg/kg) + ipilimumab (1 mg/kg) n=425†	12 months (95% CI 9 to 17)	42% (95% CI 38% to 47%)	47 months (95% CI 35 to 56) HR 0.69
	Sunitinib (control; 50 mg)	9 months (95% CI 7 to 11)	27% (95% CI 23% to 32%)	26 months (95% CI 22 to 33)
	n=422†			

Trials presented in order of regimen approval within the combination subcategories (ie, ICI plus TKI, then dual ICI).

*Clinical trial primary endpoints.

†Patients with IMDC intermediate-risk or poor-risk RCC were assessed for the primary endpoints of this study.

ccRCC, clear-cell RCC; f/u, follow-up; ICI, immune checkpoint inhibitor; IMDC, International Metastatic RCC Database Consortium; mg, milligram; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.

Initial assessment

Imaging

Beyond the diagnostic imaging discussed in the **General diagnostic tests and staging** section, patients with newly

diagnosed metastatic disease should undergo brain imaging to assess for central nervous system (CNS) metastasis; in select cases, MRI may be warranted. Early identification is important to facilitate appropriate

metastases-directed therapies, as ICI therapy has only shown modest activity in RCC brain metastases.¹¹⁴

Risk models

The IMDC classification system and the MSKCC/Motzer Score for metastatic RCC were developed as prognostic tools for patients with metastatic RCC by combining independent prognostic factors (clinical and laboratory) for survival into scoring systems.^{19 115 116} See the **General diagnostic tests and staging** section for more information on the various risk models for RCC. However, these risk models were developed and validated before the approved ICI combinations became the SOC for metastatic RCC. As such, their predictive accuracy for ICIs is limited.

Consideration for cytoreductive nephrectomy and SBRT

Cytoreductive nephrectomy (CN), also known as debulking nephrectomy, was previously the established SOC in metastatic RCC before initiating TKI monotherapy or as a deferred treatment after a limited number of cycles of TKIs with no progression (based on results from the SURTIME and CARMENA trials).^{117 118} However, since the treatment landscape has shifted to first-line immunotherapy combinations, the role of CN has become unclear and is under active investigation.¹¹⁹ In general, there has been a movement away from upfront CN with the exception of select cases. Data for deferred CN is still evolving and being assessed in prospective trials. While prospective data are limited at the time of guideline publication, two randomized phase III trials, NORDIC-SUN (NCT03977571) and PROBE (NCT04510597), and the phase II Cyto-KIK trial (NCT04322955), are evaluating the combination of ICI-based therapies with or without deferred CN.^{120–122} Some studies have reported on the efficacy of CN in patients after they have received an ICI-based first-line therapy, but the data thus far for ICI therapy before CN are limited to case studies and retrospective analyses.^{119 123} Decisions regarding CN for patients with metastatic RCC who will receive an ICI-based combination should be done in consultation with a multidisciplinary team and may be based on a variety of factors including the patient's performance status, the amount of overall disease that is located within the primary tumor, and whether there is symptomatic disease, sarcomatoid differentiation, visceral involvement (bone, liver or brain), and/or a need to alleviate symptoms associated with the primary tumor. The role of stereotactic body radiation therapy (SBRT) is also under active investigation in combination with immunotherapy compared with ICI therapy alone in patients with metastatic RCC in two phase II trials, CYTOSHRINK (NCT04090710)¹²⁴ and SAMURAI/NRG-GU012 (NCT05327686).¹²⁵

Available immunotherapy combinations for treatment-naïve ccRCC

ICI plus TKI combination therapy

On April 19, 2019, pembrolizumab plus axitinib was approved for the first-line treatment of advanced ccRCC based on data from the phase III randomized KEYNOTE-426 trial (NCT02853331). The trial enrolled 861 patients (randomized 1:1) with newly diagnosed or recurrent stage IV ccRCC with no previous systemic therapy to receive pembrolizumab plus axitinib (pembrolizumab was stopped after 2 years) or sunitinib. At the time of approval, pembrolizumab plus axitinib demonstrated significantly improved PFS (HR 0.69; 95% CI 0.57 to 0.84; $p < 0.001$) and OS (HR 0.53; 95% CI 0.38 to 0.74; $p < 0.0001$) compared with sunitinib.^{10 62} In the 43-month follow-up analysis, the mOS and median PFS (mPFS), which were immature at the time of approval, were reported along with the ORR (table 2), with improvements in mOS and mPFS in the pembrolizumab plus axitinib group compared with the sunitinib group.¹²⁶ At the 5-year follow-up analysis (median follow-up 67.2 months), the 60-month OS rate for pembrolizumab plus axitinib versus sunitinib was 41.9% versus 37.1% and the 60-month PFS rate was 18.3% versus 7.3%, respectively.¹²⁷ The median duration of response (DOR) was 23.6 months (range 1.4+ to 68.6+) for pembrolizumab plus axitinib and 15.3 months (range 2.3–68.3) for sunitinib. The occurrence of grade ≥ 3 AEs of any cause occurred in 75.8% of patients treated with pembrolizumab plus axitinib, and in 70.6% of patients treated with sunitinib, with 62.9% and 58.1% of grade ≥ 3 AEs being attributed by the investigator to trial treatment, respectively.¹⁰ The most common AEs in both treatment arms were diarrhea and hypertension. In the pembrolizumab plus axitinib group, four patients (0.9%) died from TRAEs, compared with seven patients (1.6%) in the sunitinib group.

On January 22, 2021, nivolumab plus cabozantinib was approved for first-line treatment of advanced ccRCC based on data from the phase III randomized CheckMate 9ER trial (NCT03141177), demonstrating significant improvements in PFS (primary endpoint; HR 0.51; 95% CI 0.41 to 0.64; $p < 0.001$), OS (HR 0.53; 95% CI 0.38 to 0.74; $p < 0.0001$), and ORR compared with sunitinib.^{11 128} The trial enrolled 651 patients (randomized 1:1) with previously untreated advanced or metastatic RCC. At the 4-year analysis (median follow-up 44.0 months), the response and survival benefits of nivolumab with cabozantinib over sunitinib were maintained in the ITT population, with a significant improvement in mPFS and mOS (table 2).¹²⁹ Responses were also more durable with the ICI combination, with a median DOR of 22.1 months (95% CI 18.0 to 26.0) compared with 16.1 months (95% CI 11.1 to 19.4) for sunitinib. Subgroup analyses across IMDC subgroups were also performed at the long-term analysis, and PFS and OS favored nivolumab plus cabozantinib over sunitinib in the intermediate, poor, and intermediate/poor risk subgroups, and higher ORR and CR rates were

observed in the nivolumab plus cabozantinib cohort across all subgroups. Treatment-free survival (TFS) was also analyzed at a 4-year follow-up, where of the surviving patients (n=640) treated with nivolumab plus cabozantinib (n=320) or sunitinib (n=320), 17.6% and 4.7% were treatment-free, respectively, and the mean TFS was 2.4 months longer (7 months vs 4.6 months) following treatment with nivolumab plus cabozantinib.¹³⁰ Grade ≥ 3 TRAEs occurred in 66.9% of patients treated with nivolumab plus cabozantinib, and 55.3% of patients treated with sunitinib.¹²⁹ Immune-mediated AEs in both groups were mostly low-grade and managed with corticosteroids.¹³¹ The most common grade ≥ 3 immune-mediated AEs were increased alanine aminotransferase (3%), diarrhea (3%), and hepatotoxicity (2%). Overall, one treatment-related death occurred in the nivolumab plus cabozantinib group, whereas three treatment-related deaths occurred in the sunitinib group.^{11 131}

On December 27, 2024, nivolumab plus hyaluronidase-nvhy was approved for subcutaneous injection for adults across all solid tumor indications for nivolumab.¹³² Additionally, on September 19, 2025, pembrolizumab and berahyaluronidase alfa-pmph was also approved for subcutaneous injection for adult and pediatric patients across all solid tumor indications for pembrolizumab.¹³³ Subcutaneous delivery provides an alternative administration option for both agents and has practical advantages; however, the change in administration route does not diminish the need for vigilant monitoring of patients for irAEs. Monitoring should remain consistent with established protocols for intravenous nivolumab. Clinicians should be aware of this administration option when making treatment decisions.

On August 10, 2021, pembrolizumab plus lenvatinib was approved for first-line treatment of advanced ccRCC based on data from the phase III randomized CLEAR trial (Study 307/KEYNOTE-581; NCT02811861). The trial enrolled 1,069 patients with previously untreated advanced ccRCC to be randomized 1:1:1 to receive either pembrolizumab plus lenvatinib, everolimus plus lenvatinib, or sunitinib monotherapy, though the approval was based on analyses between the pembrolizumab combination and sunitinib groups. At the time of approval, pembrolizumab plus lenvatinib demonstrated significantly improved PFS (primary endpoint; HR 0.39; 95% CI 0.32 to 0.49; $p < 0.001$) and OS (HR 0.66; 95% CI 0.49 to 0.88; $p = 0.005$) compared with sunitinib alone.^{12 62} With more mature data in the 4-year follow-up analysis, the PFS and OS benefit was maintained (table 2).¹³⁴ Subgroup analyses across IMDC and MSKCC risk groups were performed, and pembrolizumab plus lenvatinib resulted in improved OS over sunitinib for poor-risk and intermediate-risk groups. OS was similar for both regimens in the favorable groups; however, the study was not powered for this analysis. PFS favored pembrolizumab plus lenvatinib across all risk groups. Grade ≥ 3 TEAEs emerged or worsened during treatment in 84.9% of patients treated with pembrolizumab plus lenvatinib versus 74.7% of patients

treated with sunitinib. Fatal TRAEs occurred in four (1.1%) and one (0.3%) patient(s), respectively.

Dual ICI combination therapy

On April 16, 2018, nivolumab plus ipilimumab was approved for intermediate-risk and poor-risk advanced RCC based on the phase III randomized CheckMate 214 trial (NCT02231749), which assessed nivolumab plus ipilimumab followed by nivolumab compared with sunitinib.^{13 128} The trial enrolled 1,096 patients (randomized 1:1) with previously untreated advanced ccRCC of any IMDC risk group; however, the primary endpoints of PFS, OS, and ORR were set to be analyzed in the IMDC intermediate-risk and poor-risk groups only, while secondary endpoints and exploratory analyses assessed efficacy in the ITT population (including IMDC favorable-risk), and in the favorable-risk groups, respectively. At the primary analysis, OS and ORR in the intermediate/poor-risk groups were significantly improved for nivolumab plus ipilimumab compared with sunitinib; however, PFS did not reach the prespecified significance threshold.¹³ While the ITT population showed significantly improved OS with nivolumab plus ipilimumab compared with sunitinib, the early exploratory OS analyses for patients with favorable-risk disease favored sunitinib. In a post hoc analysis of CheckMate 214, patients with RCC with sarcomatoid features (n=139) were analyzed. At the 6-year analysis (median follow-up 80 months), however, OS for the favorable-risk population shifted to favor nivolumab plus ipilimumab. In the favorable-risk group, mOS was 79 months (95% CI 65 to NE) for nivolumab plus ipilimumab and 68 months (95% CI 56 to 79) for sunitinib (HR 0.87; 95% CI 0.62 to 1.24). OS also continued to favor nivolumab plus ipilimumab in the ITT population (table 2).¹³⁵ For nivolumab plus ipilimumab and sunitinib in the ITT group, mPFS was similar (table 2) but improved for nivolumab plus ipilimumab in the intermediate-risk and poor-risk group (HR 0.73; 95% CI 0.61 to 0.87). TFS was assessed at a follow-up of 42 months, where of the surviving patients, 18% treated with nivolumab plus ipilimumab and 5% treated with sunitinib were treatment-free.¹³⁶ Mean TFS was over twice as long following treatment with nivolumab and ipilimumab compared with sunitinib for patients with intermediate/poor risk (6.9 months vs 3.1 months), and three times as long for favorable-risk patients (11.0 months vs 3.7 months). Patients treated with nivolumab and ipilimumab experienced more time treatment-free without toxicity than those treated with sunitinib. TRAEs occurred in 93% of patients treated with nivolumab plus ipilimumab, and 97% of patients treated with sunitinib, with grade 3–4 TRAEs occurring in 46% and 63%, respectively.¹³ In total, 436 patients who received ipilimumab plus nivolumab experienced treatment-related select irAEs, and of those, 35% were administered high-dose glucocorticoids (≥ 40 mg of prednisone per day or equivalent).¹³ At the 42-month follow-up, mean TFS with grade ≥ 3 TRAEs was 0.6 months for nivolumab plus ipilimumab

versus 0.3 months for sunitinib for intermediate/poor-risk patients, and 0.9 months versus 0.3 months for favorable-risk patients, respectively, whereas mean TFS without toxicity was 6.9 months versus 2.3 months, respectively, with a difference of 4.6 months (95% CI 2.2 to 7.0).¹³⁶

Patients with sarcomatoid features demonstrated a pronounced survival benefit with ipilimumab plus nivolumab versus sunitinib in CheckMate 214. At the 42-month analysis, the mOS for patients with sarcomatoid features treated with nivolumab plus ipilimumab (n=74) was NR (95% CI 25.2 months to NR), versus 14.2 months (95% CI 9.3 to 22.9) for patients treated with sunitinib (n=65; HR 0.45; 95% CI 0.3 to 0.7; p=0.0004). PFS and ORR were similarly improved, with no new safety signals reported.⁴⁷

As no head-to-head comparisons of these four ICI-based regimens exist to favor one combination over another, patient-related, treatment-related, and disease-related factors should be considered and discussed with the patient in the shared decision-making process. As discussed in the **Initial assessment** section, the predictive power of IMDC risk groups for response to ICIs is negligible, and despite the mixed IMDC risk-based analyses done in these studies, any of the approved regimens may be considered for patients with treatment-naïve advanced/metastatic ccRCC, regardless of IMDC risk. For patients with sarcomatoid features, nivolumab plus ipilimumab is the preferred option, due to the strong responses seen in CheckMate 214. In some cases, such as certain autoimmune conditions or other contraindications to ICIs, non-ICI first-line options may be considered.¹³⁷ Additionally, for patients with asymptomatic, low-volume, and slow-growing disease, active surveillance may also be considered. The treatment algorithm in figure 2 may be used as a guide for treatment decisions.

Other regimens have been examined in phase III randomized trials, but supportive OS data are lacking or immature at the time of guideline publication. Two regimens are examining additional ICI with TKI combinations, including the phase III trial, JAVELIN Renal 101 (NCT02684006), which is comparing avelumab plus axitinib (n=442) to sunitinib (n=444) for patients with previously untreated advanced RCC. At the first interim analysis, the mPFS was significantly improved at 13.8 months with avelumab plus axitinib, as compared with 8.4 months with sunitinib (HR 0.69; 95% CI 0.56 to 0.84; p<0.001).¹³⁸ In a follow-up analysis (minimum follow-up 28 months), OS data were still immature. Another phase III trial, IMmotion151 (NCT02420821), compared atezolizumab plus bevacizumab (n=454) to sunitinib (n=461) in patients with previously untreated metastatic ccRCC. At median follow-up 15 months, mPFS in the PD-L1-positive population was 11.2 months for atezolizumab plus bevacizumab group versus 7.7 months in the sunitinib group (HR 0.74; 95% CI 0.57 to 0.96; p=0.0217); however, the mOS (median follow-up 24 months) in the ITT population did not reach significance in comparing the two regimens (HR 0.93; 95% CI 0.76 to 1.14; p=0.4751).¹³⁹

Final analysis of mOS was 36.1 months for atezolizumab plus bevacizumab versus 35.3 months in sunitinib in the ITT population and was 38.7 months versus 31.6 months, respectively, in PD-L1-positive patients,⁵³ demonstrating the importance of careful biomarker analyses in future trials.

The phase III COSMIC 313 trial (NCT03937219) examined cabozantinib in combination with nivolumab and ipilimumab versus placebo plus nivolumab and ipilimumab in patients with previously untreated IMDC intermediate-risk or poor-risk RCC. At a median follow-up of 14.9 months, the primary outcome of PFS in the first 550 randomized patients favored the cabozantinib triplet therapy (HR 0.73; 95% CI 0.57 to 0.94; p=0.01).¹⁴⁰ However, the secondary endpoint of OS in the expanded ITT population (n=855) was not met (HR 1.02; 95% CI 0.85 to 1.23; p=0.84).¹⁴¹ Grade 3–4 AEs were also increased in the triplet therapy group (81%) compared with nivolumab plus ipilimumab (62%). As such, the combination of cabozantinib with nivolumab and ipilimumab is not recommended as a first-line treatment.

Additionally, high dose (HD)-IL-2 was approved in 1992 for the treatment of patients with metastatic RCC based on a small subset of patients with tumors that had durable complete or partial responses (PR) (5%–10%).^{142–143} In prospective and retrospective studies, ORRs range from about 20%–23%.^{142–144} While high-dose (HD)-IL-2 is still an option for carefully selected patients with ccRCC, it is no longer a preferred first-line treatment, as ICI-based therapies demonstrate more robust responses and improved OS. In patients who have progressed on ICIs, a small retrospective study (n=17 with metastatic RCC) demonstrated an overall response rate of 24%, and responses were durable with over 2 years follow-up; as such, HD-IL-2 may be an option for patients who have progressed on ICIs.¹⁴⁴

Adaptive immunotherapy strategies

Adaptive immunotherapy strategies are being assessed for metastatic RCC (predominantly ccRCC), where trials are designed to allow for a change in therapy based on predetermined clinical benchmarks. There are several adaptive immunotherapy trials focusing on the combination and sequencing of nivolumab and ipilimumab, occasionally with the addition of a TKI. The phase III trial PDIGREE (NCT03793166) is examining treatment of patients with ccRCC with induction nivolumab plus ipilimumab, with response-based follow-up therapy options including cabozantinib (patients with progression of disease [PD]), nivolumab (patients with complete response [CR]), or randomization to nivolumab or combination nivolumab plus cabozantinib (patients with non-CR/non-PD).¹⁴⁵ Additionally, there are three phase II trials, OMNIVORE (NCT03203473), HCRN GU 16–260 (NCT03117309), and TITAN-RCC (NCT02917772) that have examined nivolumab induction followed by ipilimumab or nivolumab plus ipilimumab based on different response criteria. Overall, the results of these phase II

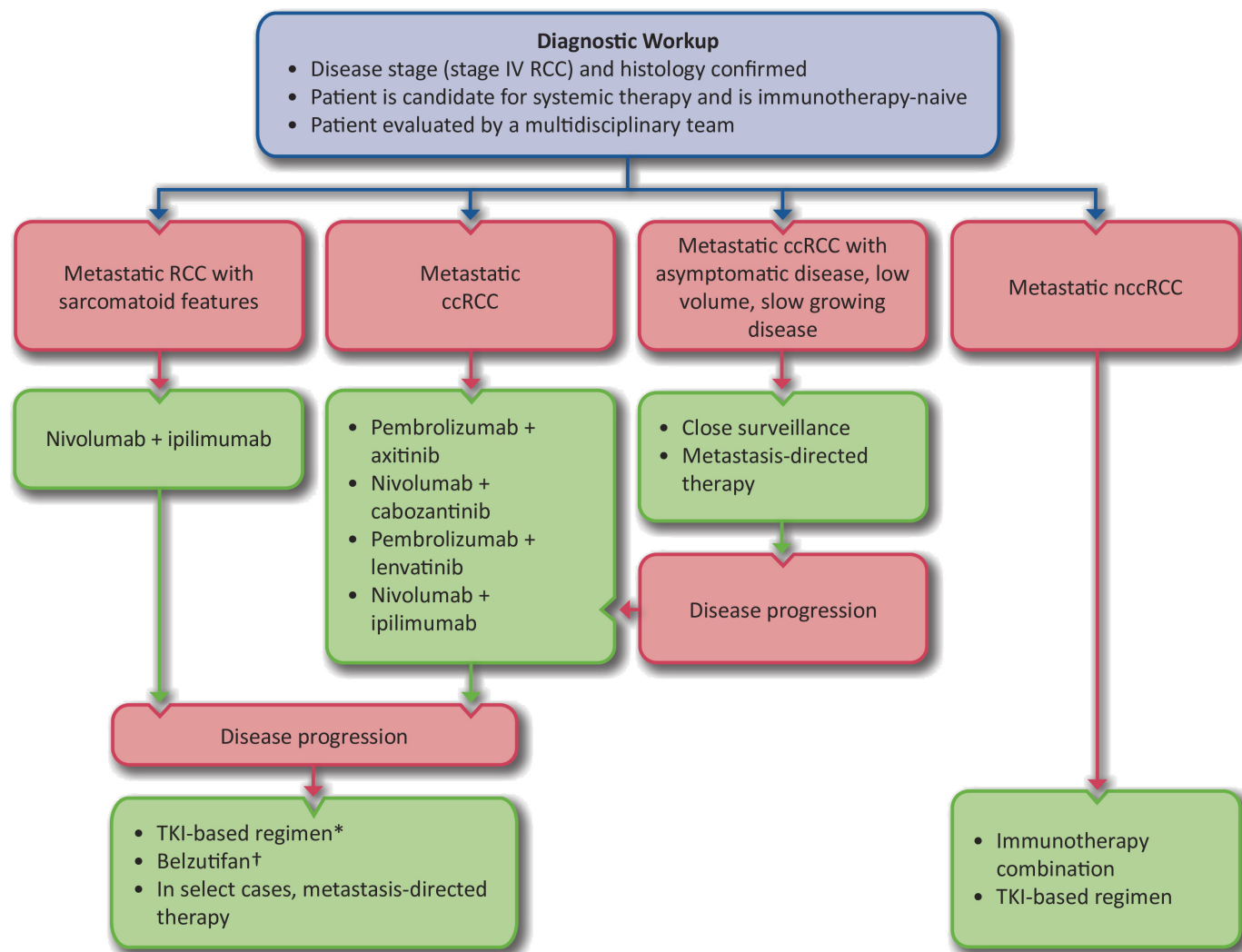


Figure 2 Immunotherapy treatment algorithm for patients with stage IV RCC. In all clinical settings, clinical trial enrollment is the preferred option, when available.

***In the setting of previous treatment with an ICI+TKI combination, treatment with a different TKI should be selected.**

†In the setting of prior anti-PD-(L)1 and VEGF-TKI.

ccRCC, clear-cell RCC; ICI, immune checkpoint inhibitor; nccRCC, non-clear cell RCC; PD-(L)1, programmed cell death protein 1 and its ligand; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

trials demonstrated that initial treatment with single-agent nivolumab or pembrolizumab (KEYNOTE-427) has less activity in patients with advanced RCC than the ICI-based combination regimens, and as such, patients should receive one of the approved ICI-based combinations (see [table 2](#)) as the front-line treatment versus an adaptive immunotherapy approach.

Available immunotherapy for previously treated RCC

Nivolumab is currently the only immunotherapy approved as a second-line therapy for patients with advanced RCC.^{128 146} It was approved on November 23, 2015, for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy, based on efficacy data from the phase III randomized Check-Mate 025 trial (NCT01668784). In this study, mOS for

nivolumab (n=410) was 25.0 months versus 19.5 months for everolimus (n=411; HR 0.73; 95% CI 0.60 to 0.89).

Due to the shift in the primary treatment landscape since this approval, however, prospective data are needed to determine the best second-line treatment following progression on or after one of the approved ICI-based regimens. Several phase III trials have conclusively demonstrated that there is no benefit to adding an ICI to a VEGFR TKI in patients with advanced RCC who progressed on a prior ICI-containing therapy. In CONTACT-03 (NCT04338269), cabozantinib with or without atezolizumab was examined in patients with locally advanced metastatic RCC (ccRCC and nccRCC) with disease progression on ICIs.¹⁴⁷ Results showed that among the two treatment groups, there was similar progression of disease, and no improvement in mPFS

with the addition of atezolizumab. Additionally, there was an increase in toxicity. TiNivo-2 (NCT04987203), a phase III randomized study, examined nivolumab plus tivozanib compared with tivozanib alone. Among patients previously treated with an ICI, there was no improvement in PFS in the patient group receiving the combination therapy versus tivozanib monotherapy, and the trial failed to meet its primary endpoint.¹⁴⁸ Data for later-line CTLA-4 inhibition is limited to the Fast Real-time Assessment of Combination Therapies in Immuno-ONcology (FRACTION)-RCC trial (n=46), which demonstrated an ORR of 17.4% (95% CI 7.8% to 31.4%), an stable disease (SD) rate of 41.3%, and mOS of 23.8 months (95% CI 13.2 to NR) in patients who progressed during or after prior immunotherapy that did not include a CTLA-4 ICI.¹⁴⁹

Taken together, sequential immunotherapy strategies have demonstrated limited activity. Patients who are refractory to first-line ICI therapy may be treated with a TKI-based regimen, and those refractory to a TKI may consider belzutifan for next-line therapy. Additionally, clinical trial enrollment is encouraged in this setting. When patients are refractory to an ICI plus TKI combination therapy, a different TKI should be selected for the second-line treatment.

Available immunotherapy for nccRCC

Despite the success of ICI-based combinations in improving survival outcomes for patients with ccRCC, immunotherapy has been less effective for nccRCC, though their inclusion in landmark trials has been limited and with low patient numbers. Of the nccRCC histologies, papillary nccRCC has the most robust data for systemic treatment options, including some evidence of activity for ICI plus VEGFR TKI combinations (see the **ICI combination therapy for nccRCC** section below), though the combinations have not been shown to be superior to VEGFR TKI monotherapy. As a result, clinical trial enrollment remains a priority regardless of histology, as SOC options are lacking. The limited data from complete or ongoing studies assessing ICI efficacy (at the time of guideline publication) in patients with nccRCC are outlined in this section.

ICI monotherapy for nccRCC

ICI monotherapy has been assessed in patients with nccRCC in a few small studies, with variable results. In the phase IIIb/IV CheckMate 374 (NCT02596035) study, the nccRCC population consisted of 24 papillary, 7 chromophobe, 8 unclassified, and 5 other non-clear cell histologies.³¹ At median follow-up of 11 months (range 0.4–27) following flat-dose nivolumab, ORR was 13.6% (95% CI 5.2% to 27.4%), with 1 CR in a patient with chromophobe histology, and 5 PRs in papillary (n=2), chromophobe (n=1), collecting duct (n=1), and unclassified (n=1) histologies. Patients with sarcomatoid features made up 9.1% of the treatment population. Median PFS

was 2.2 months (95% CI 1.8 to 5.4), and mOS was 16.3 months (95% CI 9.2 to NE). Additionally, a phase II study, HCRN GU16-260-Cohort B (NCT03117309), examined nivolumab and salvage nivolumab plus ipilimumab in patients with treatment-naïve advanced nccRCC (n=35; 54% papillary, 17% chromophobe, 29% unclassified).³² Following first-line nivolumab monotherapy, mPFS was 4.0 months (95% CI 2.7 to 4.3). Although 32 patients had PD or prolonged SD, making them eligible for salvage nivolumab plus ipilimumab, only 17 patients continued to salvage therapy (due to various reasons including toxicity), with one PR. Pembrolizumab was also examined as a first-line immunotherapy in patients with treatment-naïve advanced nccRCC (n=165; 71.5% confirmed papillary, 12.7% had chromophobe, and 15.8% had unclassified RCC histology) in the single-arm, phase II KEYNOTE-427 (NCT02853344) study.³³ In all patients, the ORR was 26.7%, mPFS was 4.2 months (95% CI 2.9 to 5.6), and the mOS was 28.9 months (95% CI 24.3 months to NR). By histology, the ORRs for patients with papillary, chromophobe, and unclassified histology were 28.8% (95% CI 20.8% to 37.9%), 9.5% (95% CI 1.2% to 30.4%), and 30.8% (95% CI 14.3% to 51.8%), respectively. For patients with sarcomatoid differentiation (n=38), the ORR was 42.1% (95% CI 26.3% to 59.2%), demonstrating a potentially consistently strong response to ICIs in those with sarcomatoid features, regardless of histology.

ICI combination therapy for nccRCC

Several phase II trials and one observational trial have examined ICI combination therapies in patients with nccRCC (table 3). In all the ICI combination therapies assessed and reported in table 3, responses were observed, with the exception of cabozantinib plus nivolumab in patients with chromophobe RCC.^{34–36 150 151} Patients treated with ICI combination therapy for tumors with sarcomatoid features responded similarly to or better than those without sarcomatoid features. In the single randomized trial that enrolled patients with nccRCC, treatment with nivolumab plus ipilimumab demonstrated similar ORR compared with SOC, and a significant increase in the 12-month OS rate (table 3).¹⁵¹ Patients with papillary high-risk status treated with nivolumab plus ipilimumab saw the greatest improvement in mOS compared with SOC. To date, this is the first randomized data of combination immunotherapy in nccRCC.

Ongoing ICI trials for patients with nccRCC

There are several ongoing trials examining ICI combinations in patients with advanced nccRCC. A phase II trial assessing pembrolizumab plus axitinib, PAXIPEM (NCT05096390), was recruiting participants at the time of guideline publication. Nivolumab is also under active investigation in combination with TKIs in the phase III STELLAR-304 (NCT05678673) trial.¹⁵² Two more

Table 3 Trial data of ICI combination therapy for nccRCC

Trial and data analysis	Agent(s) investigated	Patient characteristics	Study endpoints		
			Median PFS	ORR	Safety*
CheckMate 920 (NCT02982954) ³⁵	Ipilimumab plus nivolumab (n=52; 46 assessed for response)	Previously untreated	3.7 months (95% CI 2.7 to 4.6)	19.6% (95% CI 9.4% to 33.9%)	Grade ≥3 immune-mediated AEs within 100 days of last dose: 36.5%
Phase IIIb/IV non-randomized		Sarcomatoid features: 28.8%		Sarcomatoid: 35.7% (95% CI 12.8% to 64.9%)	
Median f/u 19.0 months		Unclassified: 42.3% Papillary: 34.6% Chromophobe: 13.5% Translocation: 3.8% Collecting duct: 3.8% Renal medullary: 1.9%		Non-sarcomatoid: 12.5% (95% CI 3.5% to 29.0%)	
			Median PFS	ORR	12-month OS rate*
SUNNIFORECAST (NCT03075423) ¹⁵¹	Nivolumab plus ipilimumab (n=157)	Systemic therapy naïve	5.09 months (2.91 to 6.05)	25.4% (95% CI 15.8% to 37.1%)	86.9% (95% CI 80.2% to 91.5%) p=0.014
Phase II randomized	SOC (n=152)	Papillary (n=178) Chromophobe (n=60) Translocation (n=12) Collecting duct carcinoma (n=9) Other (n=50)	5.55 months (5.29 to 7.21)	23.3% (95% CI 15.1% to 33.4%)	76.8% (95% CI 68.6% to 83.1%)
			Median PFS	ORR*	Safety
NCT03635892 ³⁴	Cabozantinib plus nivolumab cohort 1 (n=40)	0–1 prior systemic therapy	12.5 months (95% CI 6.3 to 16.4)	47.5% (95% CI 31.5% to 63.9%)	Grade 3–4 TRAEs: 32%
Phase II non-randomized		Papillary (n=32) Unclassified (n=6) Translocation-associated (n=2)		Papillary: 47% (95% CI 29% to 65%).	
Median f/u 13.1 months		Cabozantinib plus nivolumab cohort 2 (n=7)	0–1 prior systemic therapy Chromophobe (n=7)		
			Median PFS*	ORR	Safety
Meet-URO 23 ¹⁵⁰	Pembrolizumab plus axitinib (n=32)	Patients with nccRCC enrolled in I-RARE	10.8 months (95% CI 1.7 to 11.5)	43.7%	Interruption of treatment due to irAEs: 34.3%
Observational study		Papillary (n=19) Chromophobe (n=13)		Papillary: 47.3%	
Data collection December 2020 to April 2022				Chromophobe: 41.6%	

Continued

Table 3 Continued

			Median PFS	Confirmed OR*	Safety
KEYNOTE-B61 (NCT04704219) ³⁶ Phase II non- randomized	Pembrolizumab plus lenvatinib (n=158)	Previously untreated	18 months (95% CI 14 to NR)	49% (95% CI 41% to 57%)	Any grade TRAE: 94%
Median f/u 14.9 months		Sarcomatoid features (n=19) Papillary (n=93) Chromophobe (n=29) Unclassified (n=21) Translocation (n=6) Other (n=9)		Papillary: 54% (95% CI 43% to 64%) Chromophobe: 28% (95% CI 13% to 47%) Unclassified: 52% (95% CI 30% to 74%) Translocation: 67% (95% CI 22% to 96%) Other: 56% (95% CI 21% to 86%)	Grade 3–4 TRAE: 51% AE deaths: 5%

Trials are presented in order of trial start date, when available.

*Primary endpoint.

TRAE, treatment-related adverse events; AEs, adverse events; f/u, follow-up; ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; I-RARE, Italian Registry on RAre genitor-uRinary nEoplasms; nccRCC, non-clear cell renal cell carcinoma; NR, not reached; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

randomized combination trials are actively recruiting, the phase II trial PAPMET2 (NCT05411081) for the analysis of cabozantinib with or without atezolizumab,¹⁵³ and the phase III trial SAMETA (NCT05043090) for the analysis of savolitinib with durvalumab,¹⁵⁴ both in patients with papillary RCC.

Expert Panel recommendations

Initial assessment

- ▶ For patients who are candidates for immunotherapy with metastatic RCC, the role of cytoreductive nephrectomy or SBRT to the renal primary is under active investigation. In the absence of definitive prospective data, a multidisciplinary approach is recommended for consideration of cytoreductive nephrectomy either in an immediate or deferred fashion (LE:3).
- ▶ For patients eligible for systemic therapy, an immunotherapy-based approach is recommended (LE:1).
- ▶ A subset of patients with asymptomatic, low-volume, and slow-growing disease could be candidates for active surveillance or metastases-directed therapy (LE:3).

Available immunotherapy for treatment-naïve ccRCC

- ▶ For patients with sarcomatoid features with RCC, ipilimumab plus nivolumab is a preferred option (LE:1).
- ▶ For patients being considered for an immunotherapy-based approach, four regimens (nivolumab plus ipilimumab; pembrolizumab plus axitinib; nivolumab plus cabozantinib; pembrolizumab plus lenvatinib) have been shown to improve OS. In the absence of

head-to-head comparisons any of these options is recommended (LE:1).

- ▶ For patients with treatment-naïve metastatic RCC, clinical trial enrollment should be encouraged, when available.

Available therapy for previously treated disease

- ▶ For patients with ICI-refractory metastatic RCC, a TKI-based regimen or belzutifan (in the setting of prior TKI) is recommended (LE:3). If the patient previously received an ICI plus TKI combination, treatment with a different TKI should be selected.
- ▶ There is no proven role for sequential anti-PD-(L)1 regimens for patients with previously treated metastatic RCC.
- ▶ For patients with previously treated metastatic RCC, clinical trial enrollment should be encouraged.

Available immunotherapy for treatment-naïve nccRCC

- ▶ For patients with treatment-naïve nccRCC, enrollment on a clinical trial is recommended when available.

SPECIAL CONSIDERATIONS FOR ICI TREATMENT

RCC-specific considerations for ICI treatment

Hereditary RCC

RCC can be associated with several autosomal dominant hereditary disorders. For example, about 30%–60% of individuals with von Hippel-Lindau (VHL) disease will develop RCC.^{155 156} Data for ICI treatment of VHL-associated RCC are limited as patients were not represented in landmark clinical trials. Currently, the SOC treatment is belzutifan, which was FDA-approved for adult patients with VHL disease and associated RCC,

CNS hemangioblastomas, or pancreatic neuroendocrine tumors that require treatment but not immediate surgery.^{157 158} Due to the lack of data on efficacy of ICIs for VHL-associated RCC, guideline-directed systemic treatment options and sequencing should be used.^{137 159}

Brain or bone metastases

Approximately 10%–16% of patients with RCC develop brain metastases.^{160 161} Additionally, RCC often metastasizes to the bones¹⁶² and liver. Patients with bone metastases have experienced poorer survival in response to ICI therapy compared with those without bone metastases.¹⁶³ Bone-targeting agents in conjunction with systemic therapy have been shown to improve outcomes and should be considered for patients with bone metastases.¹⁶⁴ Patients with brain metastases were often excluded from the landmark ICI phase III trials; however, a few have included patients with asymptomatic brain metastases and reported subgroup analyses. Cohort 3 of the CheckMate 920 trial (NCT02982954) examined nivolumab plus ipilimumab followed by nivolumab in patients with previously untreated advanced RCC with asymptomatic brain metastases (n=28).¹⁶⁰ At a minimum follow-up of 24.5 months the ORR was 32% (95% CI 14.9% to 53.5%), with all PRs. In those that responded, the median DOR was 24 months. At the time of follow-up, four of the eight responders had not reported progression of disease. Within the entire treatment cohort of 28 patients, seven patients experienced intracranial progression, five of whom only had intracranial progression, and two of whom had intracranial and systemic progression. No new safety signals were observed in this patient population. Nivolumab monotherapy was assessed in the phase II non-controlled GETUG-AGU 26 NIVOREN study (NCT03013335) in patients with metastatic RCC. A cohort analysis was done on the patients with asymptomatic brain metastases (n=73), and of the patients with ccRCC and previously untreated brain metastases the intracranial response rate was 12% and the median intracranial PFS was 2.7 months (95% CI 2.3 to 4.6). In patients who had received a prior treatment for brain metastases, intracranial PFS was 4.8 months (95% CI 3.0 to 8.0).¹¹⁴

Oligoprogressive and oligometastatic disease

Patients with oligoprogressive or oligometastatic disease may require additional considerations and treatment of the metastatic lesions, most often with localized therapies. Increasing evidence supports the use of local therapies (eg, SBRT, resection, ablation) to manage metastatic lesions; however, observation (in select cases for slow-growing or asymptomatic lesions) can also be considered.^{165 166} Importantly, treatment with local therapies does not require interruption of systemic therapy, including ICI-based regimens. The phase I/II RAPPORT trial (NCT02855203) assessed SBRT followed by a short course of pembrolizumab in patients with oligometastatic ccRCC. Safety analyses demonstrated a low level of grade 3 AEs (13%) and no grade 4–5 AEs.¹⁶⁷ For oligoprogressive

disease, while the data are limited, the summary of these studies demonstrates that ICIs used concurrently with local therapies (eg, SBRT, resection, ablation) is a safe and effective strategy.¹⁶⁸ Consultation with a multidisciplinary team is recommended to coordinate the best treatment options for these patients.

Response monitoring and treatment beyond progression

Due to the mechanisms of ICIs, tumor responses can be delayed compared with targeted therapy or chemotherapy.^{169 170} Therefore, additional consideration is needed when monitoring for response, especially if using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 for radiographic monitoring, which was not developed to account for immunotherapy-specific response patterns.^{171 172} One atypical response pattern reported in a small portion of patients treated with ICIs is pseudoprogression, which is apparent tumor progression followed by tumor shrinkage/response.¹⁷³ While prospective data are lacking, pseudoprogression has been reported in patients with RCC in case studies,^{174 175} and larger studies have reported an inconsistent incidence of pseudoprogression/atypical responses ranging from 1.8% to 14%.^{176 177} Pseudoprogression is rare, and integration of clinical, laboratory, and radiologic findings needs to be appropriately addressed to determine if treatment should continue in the context of suspected pseudoprogression.

In a phase II randomized trial (NCT01354431), patients with advanced/metastatic RCC who had progressed (as defined by RECIST v1.1) while being treated with nivolumab monotherapy continued treatment beyond progression (n=36) or discontinued treatment (n=92).¹⁷⁸ Of those treated beyond progression, 69% experienced subsequent tumor reduction or stabilization. Additionally, mPFS was 4.2 months (95% CI 2.8 to 5.5) in the treated beyond progression group versus 2.6 months (95% CI 1.5 to 3.9) in the group not treated beyond progression. However, TRAEs were higher in patients treated beyond progression, but that difference in incidence was lower when adjusted for length of treatment exposure. Additionally, a non-randomized subgroup analysis of the phase III CheckMate 025 trial examined patients being treated with nivolumab beyond RECIST v1.1 progression. Patients received nivolumab for ≥4 weeks after initial progression,¹⁷⁹ and patients not treated beyond progression were treated <4 weeks after initial progression. Of all the patients treated post-progression, 13% had a ≥30% reduction in tumor burden. The incidence of any grade TRAEs in patients treated beyond progression was lower following progression (59%) compared with before progression (71%). Although data are limited, due to the possibility for pseudoprogression or delayed responses, in addition to other clinical benefits of treatment with ICIs, treatment beyond apparent progression (defined by RECIST v1.1) may be considered in select cases, with more frequent scans to monitor status. Of note, response criteria have been developed that account for atypical response patterns seen with ICIs, such as immune-related

RECIST (irRECIST),¹⁸⁰ immune-related response criteria (irRC),¹⁷¹ immune-modified RECIST (imRECIST)¹⁸¹ and immune RECIST (iRECIST);¹⁷² however, uptake of these criteria in clinical trials has been slow.

Duration of treatment

Research is ongoing to determine the optimal duration of ICI treatment that will drive the most effective and durable anti-tumor responses while minimizing overtreatment that may result in irAEs.¹⁸² At this time, the best available evidence supports up to 2 years of ICI treatment, which has been the upper limit for duration of treatment in some landmark ICI trials for RCC, including KEYNOTE-426,¹⁰ CLEAR,¹³⁴ and CheckMate 9ER.¹¹ However, for patients who have responded or have stable disease and tolerate ICI therapy well, continuation of therapy beyond 2 years is an option. Some studies continued ICI treatment indefinitely until disease progression or toxicity, such as CheckMate 025¹⁸³ and CheckMate 214.¹³ Within these trials, many patients would receive therapy beyond 2 years, with some patients still receiving treatment at the 55-month follow-up. However, the median duration of treatment for responders at the 72-month follow-up of CheckMate 025 was 23.6 months.¹⁸⁴ Within the population who discontinued treatment for any reason at the follow-up, 29% did not require additional therapy.

General ICI considerations for special patient populations

Patients with certain conditions or considerations, such as those with severe autoimmune disease, active immunosuppression, HIV positivity, advanced age, solid organ transplants, poor Eastern Cooperative Oncology Group performance status (ECOG PS), pregnancy, or prior grade ≥ 3 irAEs have often been excluded from ICI clinical trials resulting in a lack of definitive data on safety and/or efficacy. As such, treatment decisions around patient selection and management while on ICIs are often derived from observational or retrospective studies. In general, referencing the respective package insert(s) for registrational safety data is recommended and consultation with the appropriate multidisciplinary specialties is necessary when treating these patients, along with a careful discussion with the patient regarding the risks and benefits of treatment.¹⁸⁵

For information and guidance on ICI-related irAE management, referencing existing guidelines is recommended, such as SITC's ICI-related irAE CPG¹⁸⁶ and others.^{187–188}

Patients with pre-existing autoimmune disease

Patients with autoimmune disease have historically been excluded from ICI clinical trials due to the potential for increased risk of irAEs. Indeed, patients with pre-existing autoimmune disease have a higher incidence of irAEs (including symptom flares related to their existing autoimmune disease) in response to ICI treatment; however, symptoms have been found to be manageable and response rates unaffected.^{189–192} One retrospective

study including patients with RCC (n=58) among other urological cancers treated with ICIs found the cumulative risk of exacerbation of their pre-existing autoimmune disease or new irAEs at 3 months was 45% (95% CI 35% to 54%).¹⁹¹ In another study that included patients with RCC (n=94; 12.5%) as well as other solid tumors, 65.9% of patients with autoimmune disease experienced irAEs (any grade), compared with 39.9% of patients who did not have pre-existing autoimmune disease; however, there were significant differences in incidence of grade 3–4 irAEs or response rates.¹⁹² Clinicians should consider the severity and symptoms of the autoimmune disease when discussing risks and benefits with patients. An ongoing phase Ib clinical trial (NCT03816345) is examining nivolumab monotherapy in patients with autoimmune disorders and advanced malignancies, with the primary outcome to measure safety and secondary outcomes measuring efficacy.

Patients who are immunosuppressed/solid organ transplant recipients

While data are limited in patients with RCC, some retrospective studies have shown reduced OS and PFS with ICIs in patients receiving systemic baseline corticosteroids with other types of cancers, including non-small cell lung cancer and melanoma.^{193–195} Interestingly, corticosteroids for non-cancer/palliative reasons and dosages <10 mg prednisone (or equivalent) were not related to reduced efficacy.¹⁹³ In general, for patients that require ≥ 10 mg prednisone or equivalent and are unable to reduce or taper the dosage, consultation with a relevant specialist is recommended before starting ICIs. Additionally, early use of steroids after starting ICIs has been shown to reduce efficacy,^{193–195} and therefore avoiding systemic steroids early in the course of treatment is recommended when clinically feasible.

Patients on immunosuppressants following a solid organ transplant have been shown to be at risk for allograft rejection with ICI therapy. A systematic review of case studies including 64 patients showed an overall allograft rejection rate of 41% in organ transplant recipients following ICI therapy.¹⁹⁹ Factors such as type of cancer, type of allograft, type of immunosuppression, time since transplantation to initiation of ICI, and prior history of rejection were not stratified in this study. Although limited to patients with kidney transplants, a small study (n=17) demonstrated that maintaining baseline corticosteroids in patients being treated with nivolumab for advanced solid tumors may reduce the risk of allograft rejection;²⁰⁰ however, more studies are needed to understand the risks of this approach. With the high potential for allograft rejection, all available treatment options and their risks/benefits should be thoroughly discussed with patients in consultation with the transplant service.

Patients living with HIV

Patients living with HIV (PLWH) are at a higher risk of developing certain malignancies, including RCC.²⁰¹ One non-randomized phase I trial with 30 participants showed that patients with HIV and a CD4 count of >100 cells/μL had an acceptable safety profile when treated with pembrolizumab.²⁰² Additional retrospective analyses also concluded that ICI therapy for PLWH is effective and does not pose an increased risk for irAEs.^{203 204} While studies are needed to confirm this in patients with RCC, HIV positivity is not currently a contraindication to ICI therapy.

Patients who are older adults or have an ECOG PS ≥2

Although ICIs are often considered more tolerable than other treatments such as chemotherapy, irAEs are still a concern for patients who are frail. A retrospective analysis comparing cohorts of <65 years (n=185), 65–74 years (n=154) and ≥75 years (n=109) showed that there was no overall difference in the incidence of grade ≥3 AEs from ICI therapy across age groups.^{205 206} Notably, dermatologic AEs were more common in older cohorts, whereas endocrine-related AEs were less common.^{205 206} Overall, age is not a contraindication for ICIs,^{207 208} and outcomes appear to be similar in older groups compared with younger groups.²⁰⁷ A comprehensive geriatric assessment for older patients to ensure they are fit enough to endure potentially severe irAEs may be considered.¹⁸⁵

Patients with metastatic RCC with ECOG PS ≥2 (n=56) were assessed in a retrospective study examining first-line ICI therapy combinations of nivolumab plus ipilimumab or pembrolizumab plus axitinib.²⁰⁹ At the median follow-up of 11.1 months, there was no significant difference in ORR between the two regimens, though ORR was numerically higher for pembrolizumab plus axitinib (42%). In total, 45% of patients had died at the time of analysis, and the incidence of grade ≥3 TRAEs was 24% for patients treated with pembrolizumab plus axitinib and 22% for patients treated with nivolumab plus ipilimumab. Another retrospective study on safety and efficacy included a small cohort of patients with RCC (n=4) and showed a diminished efficacy in patients with ECOG PS ≥2 compared with patients with better PS.²¹⁰ These data demonstrate that patients with ECOG PS ≥2 may have reduced responses to ICIs, although follow-up prospective studies are needed for validation.

Patients who are pregnant or with fertility concerns

Data on ICI therapy in pregnancy are extremely limited. Case studies have demonstrated a risk for premature birth and pregnancy complications for patients who are pregnant and treated with ICIs.²¹¹ The prescribing information for the approved ICIs for RCC at the time of guideline publication (pembrolizumab, nivolumab, ipilimumab) note the potential for embryo-fetal harm, and advises women of child-bearing age to use contraception during treatment

and for 3–5 months after the last dose.^{62 128 212} Fertility may be affected by the use of ICI therapies either directly or through immune-related endocrinopathies.^{213 214} As such, fertility preservation should be considered before treatment, and consultation with specialists is recommended.

Patients with prior grade ≥3 irAE(s)

For patients with recurrent and/or advanced RCC, treatment options are limited and patients may receive ICIs in multiple lines of treatment, either as a rechallenge after prior disease progression or after treatment was stopped due to toxicity. When patients have experienced a prior irAE, particularly if severe grade (≥3) or if life-threatening (eg, myocarditis), a careful risk/benefit discussion is recommended before starting a new immunotherapy regimen. Though the data are limited on the risk of recurrent irAEs in this setting, a meta-analysis of smaller studies found rechallenge with ICI to be effective but with lower safety than primary therapy.²¹⁵

Expert Panel recommendations

- ▶ Local therapy should be considered for patients with RCC with oligometastatic disease (LE:3).
- ▶ Local therapy for oligometastatic RCC does not require interruption of systemic immunotherapy.
- ▶ For patients with RCC and brain metastases, consider local therapy with or without systemic therapy whenever feasible (LE:4). Local therapy should not interrupt immunotherapy.
- ▶ For patients with RCC with oligoprogressive disease, stereotactic radiation therapy should be considered (LE:3).
- ▶ For patients with advanced RCC with radiographic progression but who remain clinically stable and are tolerating therapy, continuation of systemic immunotherapy with close monitoring may be considered (LE:2).
- ▶ For patients receiving immunotherapy for metastatic RCC, the best available evidence supports 2 years of ICI treatment (LE:2); however, treatment could be continued beyond 2 years as personalized to the patient (LE:3).
- ▶ For patients who have received local therapies to all sites of metastatic disease within 1 year of nephrectomy, adjuvant pembrolizumab treatment for 1 year can be considered (LE:2).
- ▶ For patients with pre-existing significant autoimmune disease (LE:3) or solid organ transplant (LE:4), avoiding ICI therapy initially and consulting with a specialist is recommended.
- ▶ For patients being considered for treatment with ICIs, HIV is not a contraindication (LE:3).
- ▶ For patients being considered for treatment with ICIs, older age is not a contraindication (LE:4). Geriatric assessment before initiation of ICIs therapy can be

considered to determine if patients will be able to tolerate the treatment.

PATIENT EDUCATION AND QOL

Patient education regarding ICI treatment

Immunotherapies are unique to other treatment modalities such as chemotherapy and radiation that many patients may be more familiar with, including their mechanisms of action, response patterns, side effects, financial impacts, lifestyle considerations, drug interactions, and other factors potentially impacting a patient's experience, survivorship, and QOL. Clinicians should be aware of and discuss these unique considerations with patients and their caregivers.

ICI patient/caregiver education

To ensure that patients feel involved and informed in their own treatment plan, discussion topics before starting therapy should include the expected response times to ICI-containing regimens (can be delayed compared with other types of treatment)^{169 170 173} potential short-term and long-term side effects (including life-threatening and chronic irAEs),²¹⁶ how irAEs are typically managed (temporarily withholding or stopping treatment vs dosage reduction),¹⁸⁶ and the expected timing and presentations of side effects. Additionally, educating patients on the likelihood of a long-term durable response with ICI therapy will allow them to manage expectations and ultimately reduce anxiety.²¹⁷ Education materials, including pamphlets, online videos and resources, patient-focused guidelines, and/or plain-language summaries of clinical trial outcomes should be given, when available, as resources to have on hand throughout their treatment.

Early identification and management of side effects is important to reduce treatment-related morbidity and improve QOL. Patients should be informed of symptoms and presentations of TRAEs and irAEs to monitor for at home, and when to seek medical attention.²¹⁸ This information may include call parameters for when and what healthcare providers to contact for specific symptoms (eg, oncology team, emergency care). Caregivers should be included in these conversations and be provided educational resources so that they can care for and monitor their loved one appropriately throughout treatment.

Lifestyle considerations for patients treated with ICIs

While no prospective data exist at the time of guideline publication regarding exercise and its effects on ICI efficacy, studies have shown that exercise can improve immune system function.²¹⁹ Exercise can also improve QOL for patients by reducing stress and anxiety and mitigating cancer-related fatigue.^{220–222} Exercise can also support better sleep and enhance physical function.²²³ However, exercise should be moderate, particularly before drawing blood, as over-exercise may increase creatine phosphokinase values²²⁴ and affect treatment timelines.

While the data are scant, patients with RCC receiving immunotherapy can be encouraged to consume a high-fiber diet,²²⁵ which was shown to positively impact response to immunotherapy in a small single-center study (n=128) in patients with melanoma, likely due to its positive effects on microbiome diversity. Similarly, CBM 588, a bifidogenic live bacterial product, was shown to increase microbiome diversity and improve response to combination nivolumab plus ipilimumab therapy in patients with metastatic RCC, and as such, supplementation can be considered.²²⁶ More data are needed to definitively understand the effects of these lifestyle factors on QOL or ICI responses.

Concomitant drugs/interactions

Although no drugs are currently contraindicated with ICIs at the time of guideline publication, some studies have shown negative impacts on responses to ICIs with common prescription and over-the-counter drugs. One retrospective analysis showed that antibiotic use before ICI therapy resulted in lower response rates and survival, potentially due to the effects on the microbiome.²²⁷ Proton pump inhibitors have also demonstrated a negative impact on ICI treatment response.^{228 229} While more data are needed to validate these findings, specifically in patients with RCC, careful consideration should be given to all medications and supplements before and during ICI therapy.

QOL and survivorship considerations for ICI treatment

Patients with RCC may experience physical, mental, and psychosocial distress due to their diagnosis and treatments.²³⁰ Validated patient-reported outcomes (PRO) tools have been developed to assess health-related QOL (HRQOL), such as the EuroQol Group-Five Level Version (EQ-5D),²³¹ the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30),²³² and the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI),²³³ which are often used in clinical trials and less so in standard clinical settings. Nevertheless, either formal assessments (through a validated tool) or independent assessments of physical functioning and symptoms are encouraged throughout treatment. For patients experiencing a decrease in physical functioning that is affecting their QOL, workup for immune-mediated toxicity, disease progression, or other causes should be performed.

Clinicians should frequently assess and proactively discuss patients' emotional well-being as patients with RCC have been shown to have a moderate risk for suicide.^{234 235} Moreover, ICIs are among the more expensive oncology drugs currently on the market, and the financial toxicity can be a major burden for patients and negatively impact their QOL. The financial strain from the cost of treatments and other aspects of care (eg, hospital stays, transportation to

appointments, laboratory work, other cancer-related medications) can cause symptoms of depression and/or anxiety in patients with cancer.²³⁶ Financial toxicity may also affect patient adherence to care if they cannot afford their treatments or get to appointments.²³⁷ Discussions of financial strain associated with care and referral to assistance as needed are critical to maintaining patient QOL.

A multidisciplinary approach is needed to comprehensively address patient QOL. Referrals should be made as early as possible to the appropriate supportive care specialists, including specialty care for AE management, pain management, palliative care, social work, group therapy, mindfulness practices, nutritionists, and psychology/psychiatry.^{234 235} Data suggest that early palliative care for patients with metastatic disease is associated with improved outcomes, and palliative care referral at diagnosis of advanced disease and throughout an individual's treatment course.^{238–240} While data are limited, some studies are beginning to report the long-term effects of ICIs on survivors' QOL;²⁴¹ however, as treatments continue to improve long-term survival, more data on this topic will be essential.

QOL/HRQOL outcomes from ICI clinical trials in RCC

The landmark clinical trials leading to the ICI-based approvals for the treatment of RCC have been reported on various PRO, QOL, and HRQOL assessments, often as secondary or exploratory endpoints of the studies. These assessments include EORTC QLQ-C30 Global Health Status (GHS)/QOL, FSKI-Disease Related Symptoms (DRS), FSKI-19, Functional Assessment of Cancer Therapy-General (FACT-G), and EuroQol Visual Analogue Scale (EQ VAS), among others. Overall, the HRQOL analyses from the landmark ICI trials (KEYNOTE-564,²⁴² KEYNOTE-426,²⁴³ CheckMate 9ER,^{244 245} CLEAR,²⁴⁶ and CheckMate 214²⁴⁷) demonstrate that ICI-based therapies were the same or favorable compared with their respective controls (sunitinib or placebo) in HRQOL scores, time to deterioration, and symptoms. While these formal assessment tools and questionnaires used in clinical trials may not be practical for general use, physicians should frequently assess patients for their HRQOL.

Expert Panel recommendations

- For patients with RCC receiving immunotherapy, providing educational materials about therapy risk and benefit is recommended.
- For patients with RCC receiving immunotherapy, discussion about the risks and benefits of treatment is recommended.
- For patients with a decline in QOL or physical functioning, ensure appropriate diagnostic workup for immune-mediated toxicity, disease progression, or alternative causes.

- For patients with RCC receiving immunotherapy, assessment of emotional wellbeing and referral to appropriate specialists is recommended at initial diagnosis, disease progression, and for those with long-term irAEs.

CONCLUSION

The treatment landscape for RCC is evolving as ICI therapy progresses to first-line indications in the adjuvant and metastatic settings. However, additional progress is needed as the benefit of immunotherapy for the treatment of nccRCC remains unclear, and treatment decisions for special patient populations are complex. Additionally, a subset of patients does not respond to ICIs, and while second-line options are available, it is unknown which patients will benefit most from ICI therapy. As such, future ICI trial design for RCC would benefit from defining prospective biomarkers and patient histology for subsequent analyses, as well as including special patient populations. Immunotherapy has already improved outcomes for patients with RCC, and continued research into this dynamic field can further improve the treatment landscape and reach of immunotherapy to all subsets of patients with RCC.

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