



NCCN

National Comprehensive
Cancer Network®

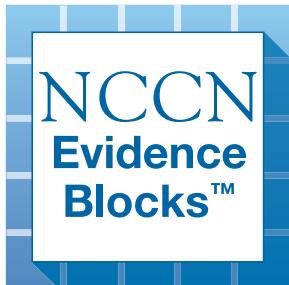
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Kidney Cancer

NCCN Evidence Blocks™

Version 2.2024 — January 3, 2024

NCCN.org



Continue



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024

Kidney Cancer

NCCN Evidence Blocks™

[NCCN Guidelines Index](#)

[Table of Contents](#)

[Discussion](#)

***Robert J. Motzer, MD/Chair † ♀**
Memorial Sloan Kettering Cancer Center

***Eric Jonasch, MD/Vice-chair †**
The University of Texas
MD Anderson Cancer Center

Neeraj Agarwal, MD ‡ †
Huntsman Cancer Institute
at the University of Utah

Ajai Alva, MBBS †
University of Michigan Rogel Cancer Center

Hilary Bagshaw, MD §
Stanford Cancer Institute

Michael Baine, MD, PhD §
Fred & Pamela Buffet Cancer Center

Kathryn Beckermann, MD, PhD †
Vanderbilt-Ingram Cancer Center

Maria I. Carlo, MD †
Memorial Sloan Kettering Cancer Center

Toni K. Choueiri, MD † ♀
Dana-Farber/Brigham and Women's
Cancer Center | Massachusetts General
Hospital Cancer Center

Brian A. Costello, MD, MS †
Mayo Clinic Comprehensive Cancer Center

Ithaar H. Derweesh, MD ω
UC San Diego Moores Cancer Center

Arpita Desai, MD † ♀
UCSF Helen Diller Family
Comprehensive Cancer Center

Yasser Ged, MBBS †
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Saby George, MD †
Roswell Park Comprehensive Cancer Center

[NCCN Guidelines Panel Disclosures](#)

John L. Gore, MD, MS ω
Fred Hutchinson Cancer Center

Andrew Gunn, MD ▲
O'Neal Comprehensive Cancer Center at UAB

Naomi Haas, MD †
Abramson Cancer Center at the University of
Pennsylvania

Michael Johnson, MD ω
Siteman Cancer Center at Barnes-Jewish
Hospital and Washington University School of
Medicine

Payal Kapur, MD ≠
UT Southwestern Simmons
Comprehensive Cancer Center

Jennifer King, MD ♀
Indiana University Melvin and Bren Simon
Comprehensive Cancer Center

Christos Kyriakopoulos, MD ‡
University of Wisconsin Carbone Cancer Center

Elaine T. Lam, MD †
University of Colorado Cancer Center

Primo N. Lara, MD †
UC Davis Comprehensive Cancer Center

Clayton Lau, MD ω
City of Hope National Medical Center

Bryan Lewis ¥
KidneyCAN

David C. Madoff, MD ▲
Yale Cancer Center/Smilow Cancer Hospital

Brandon Manley, MD ω
Moffitt Cancer Center

M. Dror Michaelson, MD, PhD †
Dana-Farber/Brigham and Women's
Cancer Center | Massachusetts General
Hospital Cancer Center

Amir Mortazavi, MD †
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Lee Ponsky, MD ω
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center
and Cleveland Clinic Taussig Cancer Institute

Sundhar Ramalingam, MD †
Duke Cancer Institute

Brian Shuch, MD ω
UCLA Jonsson Comprehensive
Cancer Center

Zachary L. Smith, MD ω
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Jeffrey Sosman, MD ‡
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Randy Sweis, MD †
The UChicago Medicine Comprehensive
Cancer Center

Matthew Zibelman, MD †
Fox Chase Cancer Center

NCCN
Lisa Gurski, PhD
Ryan Schonfeld, BA
MaryElizabeth Stein, PhD

‡ Hematology/Hematology oncology

§ Internal medicine

▲ Interventional radiology

† Medical oncology

¥ Patient advocacy

≠ Pathology

§ Radiotherapy/Radiation oncology

ω Urology

*Discussion writing committee member

[Continue](#)



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024

Kidney Cancer

NCCN Evidence Blocks™

[NCCN Guidelines Index](#)

[Table of Contents](#)

[Discussion](#)

[NCCN Kidney Cancer Panel Members](#)

[NCCN Evidence Blocks Definitions \(EB-1\)](#)

Kidney Cancer

[Initial Workup \(KID-1\)](#)

[Primary Treatment and Follow-Up for Stage I–III \(KID-1\)](#)

[Primary Treatment for Stage IV \(KID-2\)](#)

[Relapse or Stage IV Disease Treatment \(KID-3\)](#)

[General Principles of Management for Renal Cell Carcinoma \(KID-A\)](#)

[Follow-up \(KID-B\)](#)

[Principles of Systemic Therapy for Relapse or Stage IV Disease \(KID-C\)](#)

[Risk Models to Direct Treatment \(KID-D\)](#)

Hereditary Renal Cell Carcinoma

[Criteria for Further Genetic Risk Evaluation for Hereditary RCC Syndromes \(HERED-RCC-1\)](#)

[Hereditary RCC Syndromes Overview \(HERED-RCC-2\)](#)

[Genetic Testing \(GENE-1\)](#)

[Kidney-Specific Screening Recommendations for Patients with Confirmed Hereditary RCC \(HERED-RCC-B\)](#)

[Kidney-Specific Surgical Recommendations for Patients with Confirmed Hereditary RCC \(HERED-RCC-C\)](#)

[Kidney-Specific Systemic Therapy for Patients with Confirmed Hereditary RCC \(HERED-RCC-D\)](#)

[Staging \(ST-1\)](#)

[Abbreviations \(ABBR-1\)](#)

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Evidence Blocks™ and NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Evidence Blocks™, NCCN Guidelines, and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2024.

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Find an NCCN Member Institution:
<https://www.nccn.org/home/member-institutions>.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

NCCN Categories of Preference:

All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

NCCN Guidelines for Patients®
available at www.nccn.org/patients



NCCN Guidelines Version 2.2024

Kidney Cancer

NCCN Evidence Blocks™

[NCCN Guidelines Index](#)[Table of Contents](#)[Discussion](#)

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS

	E	S	Q	C	A
5					
4					
3					
2					
1					

E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Efficacy of Regimen/Agent

5	Highly effective: Cure likely and often provides long-term survival advantage
4	Very effective: Cure unlikely but sometimes provides long-term survival advantage
3	Moderately effective: Modest impact on survival, but often provides control of disease
2	Minimally effective: No, or unknown impact on survival, but sometimes provides control of disease
1	Palliative: Provides symptomatic benefit only

Safety of Regimen/Agent

5	Usually no meaningful toxicity: Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	Occasionally toxic: Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	Mildly toxic: Mild toxicity that interferes with ADLs
2	Moderately toxic: Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	Highly toxic: Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Example Evidence Block

	E	S	Q	C	A
5					
4					
3					
2					
1					

E = 4
S = 4
Q = 3
C = 4
A = 3

Quality of Evidence

5	High quality: Multiple well-designed randomized trials and/or meta-analyses
4	Good quality: One or more well-designed randomized trials
3	Average quality: Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	Low quality: Case reports or extensive clinical experience
1	Poor quality: Little or no evidence

Consistency of Evidence

5	Highly consistent: Multiple trials with similar outcomes
4	Mainly consistent: Multiple trials with some variability in outcome
3	May be consistent: Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	Inconsistent: Meaningful differences in direction of outcome between quality trials
1	Anecdotal evidence only: Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

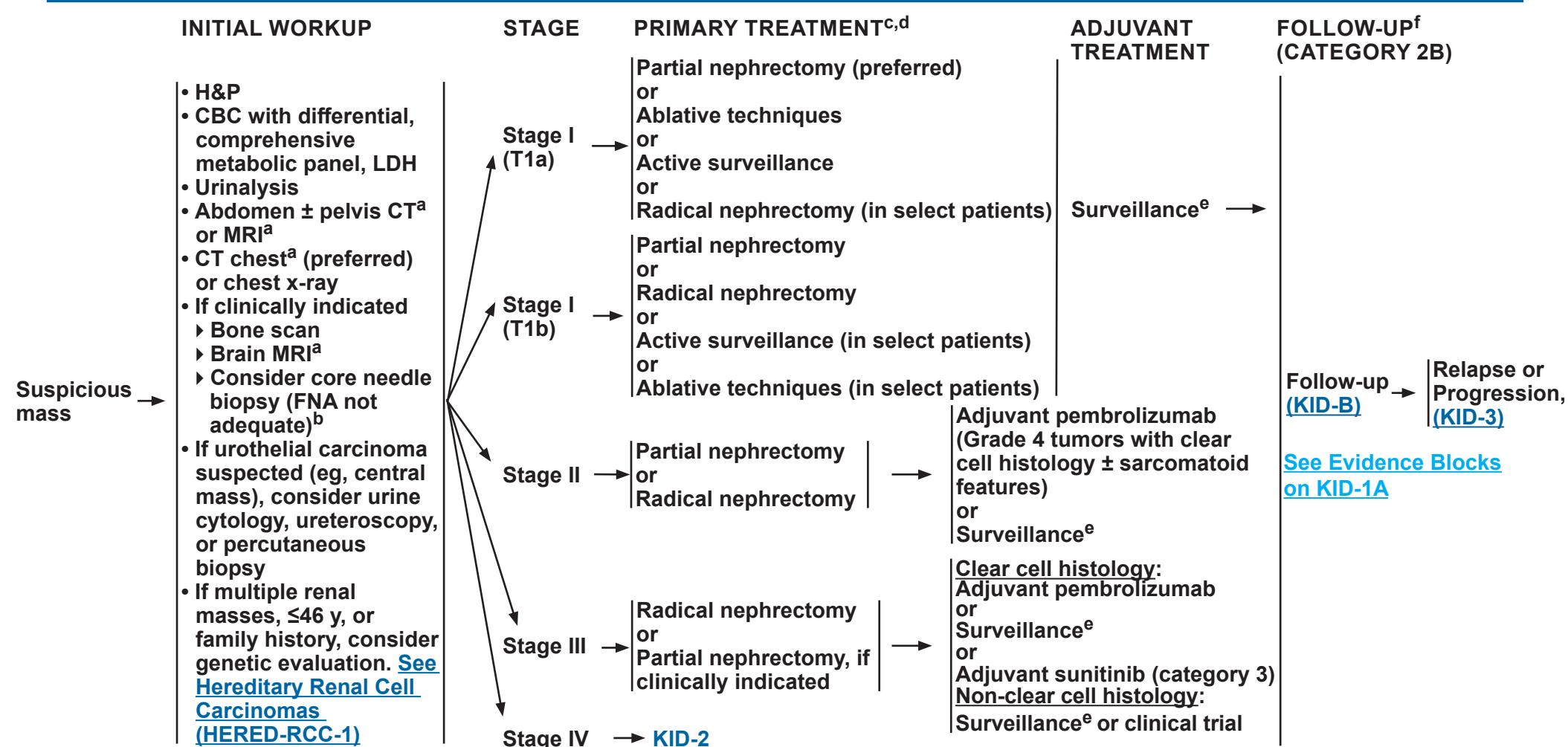
5	Very inexpensive
4	Inexpensive
3	Moderately expensive
2	Expensive
1	Very expensive



NCCN Guidelines Version 2.2024

Kidney Cancer

NCCN Evidence Blocks™



^a Imaging with and without contrast is strongly preferred, such as a renal protocol.

^b Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance or ablative techniques, cryosurgery, and radiofrequency ablation strategies.

^c [Principles of Surgery \(KID-A\)](#).

^d Stereotactic body radiation therapy (SBRT) may be considered for medically inoperable patients with stage I kidney cancer (category 2B) or with stage II/III kidney cancer (both category 3).

^e [Follow-up \(KID-B\)](#).

^f No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024

Kidney Cancer

NCCN Evidence Blocks™

5	E = Efficacy of Regimen/Agent
4	S = Safety of Regimen/Agent
3	Q = Quality of Evidence
2	C = Consistency of Evidence
1	A = Affordability of Regimen/Agent

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

EVIDENCE BLOCKS FOR SYSTEMIC ADJUVANT TREATMENT FOLLOWING NEPHRECTOMY FOR CLEAR CELL HISTOLOGY AND HIGH-RISK RENAL CELL CARCINOMA

Stage II	
Pembrolizumab	

Stage III	
Pembrolizumab	
Sunitinib	

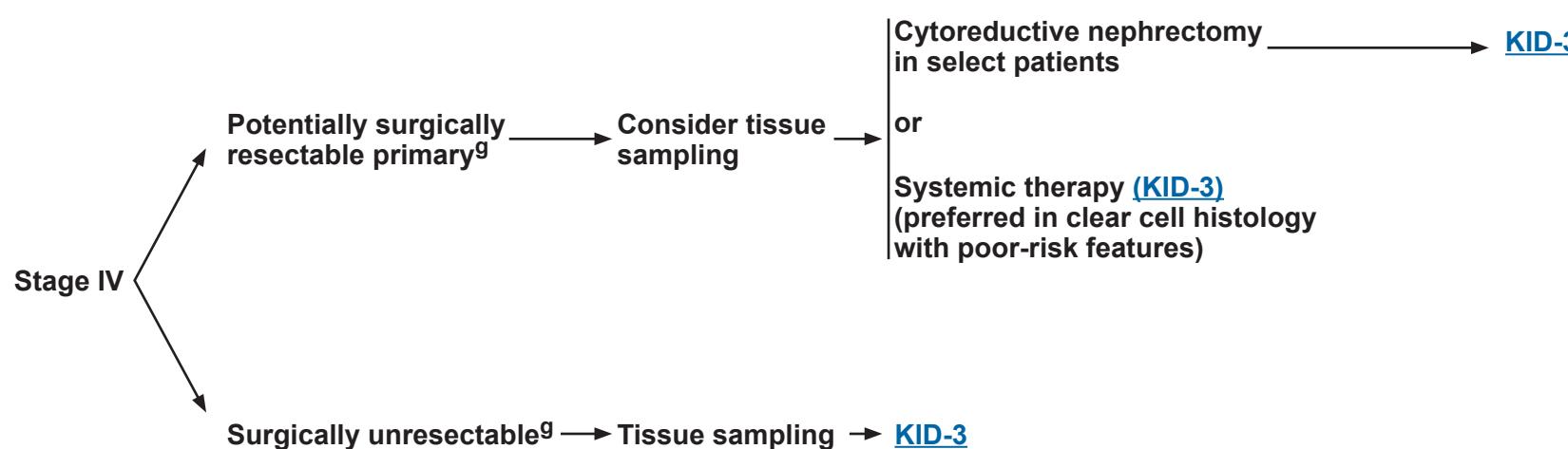
Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



STAGE

PRIMARY TREATMENT^c



^c [Principles of Surgery \(KID-A\)](#).

^g Individualize treatment based on symptoms and extent of metastatic disease.

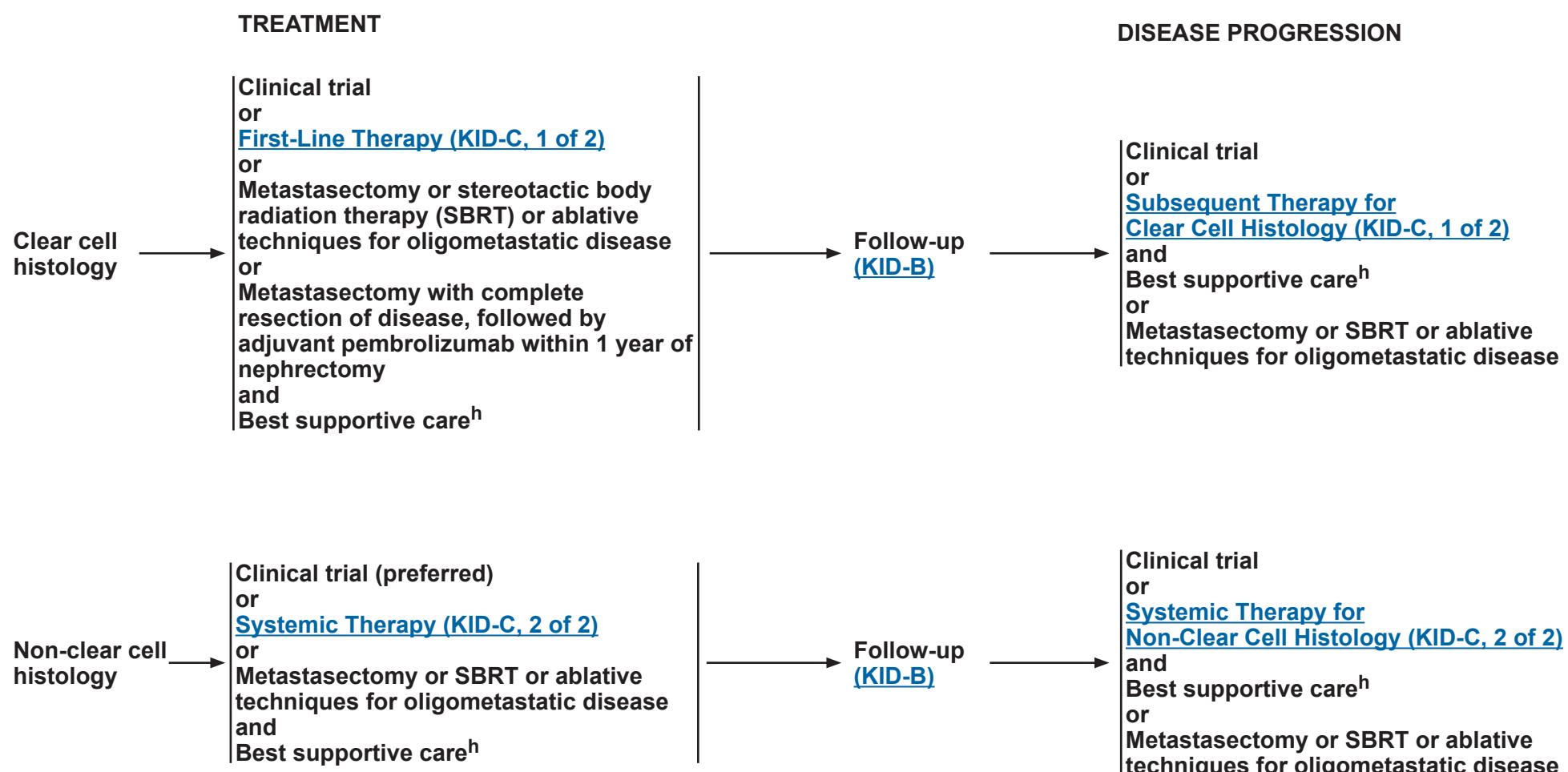
Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



RELAPSE OR STAGE IV



[See Evidence Blocks on KID-3A](#)

^h Best supportive care can include palliative radiation therapy (RT), bisphosphonates, or receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors for bony metastases.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024

Kidney Cancer

NCCN Evidence Blocks™

5		E = Efficacy of Regimen/Agent
4		S = Safety of Regimen/Agent
3		Q = Quality of Evidence
2		C = Consistency of Evidence
1		A = Affordability of Regimen/Agent

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

EVIDENCE BLOCK FOR ADJUVANT TREATMENT FOLLOWING METASTASECTOMY FOR STAGE IV RCC WITH CLEAR CELL HISTOLOGY

Pembrolizumab



Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



GENERAL PRINCIPLES OF MANAGEMENT FOR RENAL CELL CARCINOMA

- Nephron-sparing surgery (partial nephrectomy) is recommended in select patients, such as:
 - ▶ Unilateral stage I–III tumors where technically feasible
 - ▶ Uninephric state, renal insufficiency, bilateral renal masses, and familial renal cell cancer
 - ▶ Patients at relative risk for developing progressive chronic kidney disease due to young age or medical risk factors (ie, hypertension, diabetes, nephrolithiasis)
- Open, laparoscopic, or robotic surgical techniques may be used to perform radical and partial nephrectomies.
- Regional lymph node dissection is optional but should be considered for patients with resectable adenopathy on preoperative imaging or palpable/visible adenopathy at time of surgery.
- If adrenal gland is uninvolved, adrenalectomy may be omitted.
- Special teams or referral to high-volume centers may be required for extensive inferior vena cava involvement.
- Thermal ablation (eg, cryosurgery, radiofrequency ablation, microwave ablation) is an option for the management of clinical stage T1 renal lesions.
 - ▶ Thermal ablation is an option for clinical T1b masses in select patients not eligible for surgery.
 - ▶ Biopsy of lesions is recommended to be done prior to or at time of ablation.
 - ▶ Ablative techniques may require multiple treatments to achieve the same local oncologic outcomes as conventional surgery.^{a,b}
- SBRT is considered an ablative therapy and may be considered for medically inoperable patients (not optimal surgical candidates) with stage I (category 2B), II, or III (both category 3) kidney cancer ([KID-1](#)).
- Active surveillance is an option for the initial management of patients with clinical stage T1 renal lesions, for example:
 - ▶ Small renal masses <3 cm given the high rates of benign tumors and low metastatic potential of these masses.
 - ▶ Active surveillance of patients with T1a tumors (≤4 cm) that have a predominantly cystic component is recommended.
 - ▶ Patients with clinical stage T1 masses and significant competing risks of death or morbidity from intervention.
 - ▶ Active surveillance entails serial abdominal imaging with timely intervention should the mass demonstrate changes (eg, increasing tumor size, growth rate, infiltrative pattern) indicative of increasing metastatic potential.
 - ▶ Active surveillance should include periodic metastatic survey including blood work and chest imaging, particularly if the mass demonstrates growth.
- Generally, patients who would be candidates for cytoreductive nephrectomy prior to systemic therapy have:
 - ▶ Excellent performance status (ECOG PS <2)
 - ▶ No brain metastasis
- Patients either with large-volume distant metastases or tumors with large sarcomatoid burdens should receive systemic therapy prior to cytoreductive nephrectomy.

^a Campbell S, Uzzo R, Allaf M, et al. Renal mass and localized renal cancer: AUA Guideline. J Urol 2017;198:520-529.

^b Pierorazio P, Johnson M, Patel H, et al. Management of renal masses and localized renal cancer: Systematic review and meta-analysis. J Urol 2016;196:989-999.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



**FOLLOW-UP^{a,b}
(category 2B)**

Stage I

Follow-up During Active Surveillance^c

- H&P annually
- Laboratory tests annually, as clinically indicated
- Abdominal imaging:
 - Abdominal CT or MRI with and without IV contrast if no contraindication within 6 months of surveillance initiation, then CT, MRI, or ultrasound (US) at least annually
- Chest imaging:
 - Chest x-ray or CT at baseline and annually as clinically indicated to assess for pulmonary metastases
 - Consider repeat chest imaging if intervention is being contemplated
- Consider renal mass biopsy at initiation of active surveillance or at follow-up, as clinically indicated
- Follow-up may be individualized based on surgical status, treatment schedules, side effects, comorbidities, and symptoms

Follow-up After Ablative Techniques^c

- H&P annually
- Laboratory tests annually, as clinically indicated
- Abdominal imaging:
 - Abdominal CT, MRI with and without IV contrast (unless otherwise contraindicated), or contrast-enhanced US at 1–3 months, 6 months, and 12 months after ablation, then annually thereafter. If patient is unable to receive IV contrast, MRI or contrast-enhanced US are the preferred imaging modalities
 - If there is imaging or clinical concern for residual or recurrent disease, then renal mass biopsy or further treatment may be indicated
- Chest imaging:
 - Chest x-ray or CT annually for 5 years for patients who have biopsy-proven low-risk pathologic features (no sarcomatoid, low-grade [grade 1/2]) renal cell carcinoma (RCC), nondiagnostic biopsies, or no prior biopsy

^a Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.

^b No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years ([KID-B, 5 of 5](#)). Further study is required to define optimal follow-up duration.

^c CT is with IV contrast and MRI is with or without contrast.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



FOLLOW-UP^{a,b,c}
(category 2B)

Stage I

Follow-up After a Partial or Radical Nephrectomy

- H&P annually
- Laboratory tests annually, as clinically indicated
- Abdominal imaging:
 - ▶ Baseline abdominal CT or MRI (preferred) within 3–12 months of surgery, then annually for up to 5 years or longer as clinically indicated
 - ▶ A more rigorous imaging schedule can be considered if positive margins or adverse pathologic features (such as sarcomatoid, high-grade [grade 3/4])
- Chest imaging:
 - ▶ Chest x-ray or CT annually for at least 5 years, then as clinically indicated
 - ▶ A more rigorous imaging schedule (CT preferred) can be considered if positive margins or adverse pathologic features

Stage II

Follow-up After a Partial or Radical Nephrectomy

- H&P annually
- Laboratory tests annually, as clinically indicated
- Abdominal imaging:
 - ▶ Baseline abdominal CT or MRI (preferred), every 6 months for 2 years, then annually for up to 5 years or longer as clinically indicated
 - ▶ A more rigorous imaging schedule can be considered if positive margins or adverse pathologic features (such as sarcomatoid, high-grade [grade 3/4])
- Chest imaging:
 - ▶ Chest x-ray or CT annually for at least 5 years, then as clinically indicated
 - ▶ A more rigorous imaging schedule (CT preferred) can be considered if positive margins or adverse pathologic features

^a Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.

^b No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years ([KID-B, 5 of 5](#)). Further study is required to define optimal follow-up duration.

^c CT is with IV contrast and MRI is with or without contrast.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



FOLLOW-UP^{a,b,c}
(category 2B)

Follow-up for Stage III

- H&P every 3–6 months for 3 years, then annually up to 5 years, and as clinically indicated thereafter
- Comprehensive metabolic panel and other tests as indicated every 3–6 months for 3 years, then annually up to 5 years, and as clinically indicated thereafter
- Abdominal imaging:
 - ▶ Baseline abdominal CT or MRI within 3–6 months, then CT or MRI (preferred), or US (US is category 2B for stage III), every 3–6 months for at least 3 years and then annually up to 5 years
 - ▶ Imaging beyond 5 years: as clinically indicated
- Chest imaging:
 - ▶ Baseline chest CT within 3–6 months with continued imaging (CT preferred) every 3–6 months for at least 3 years and then annually up to 5 years
 - ▶ Imaging beyond 5 years: as clinically indicated based on individual patient characteristics and tumor risk factors
- Additional imaging (ie, bone scan, brain imaging):
 - ▶ As symptoms warrant

^a Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.

^b No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years ([KID-B, 5 of 5](#)). Further study is required to define optimal follow-up duration.

^c CT is with IV contrast and MRI is with or without contrast.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



**FOLLOW-UP
(category 2B)**

Follow-up After Adjuvant Therapy

- Patients who received adjuvant therapy should receive clinical follow-up as for stage III disease

Follow-up for Relapsed or Stage IV and Surgically Unresectable Disease^{c,d}

- H&P every 6–16 weeks for patients receiving systemic therapy, or more frequently as clinically indicated and adjusted for type of systemic therapy patient is receiving
- Laboratory evaluation as per requirements for therapeutic agent being used
- Chest, abdominal, and pelvic imaging:
 - ▶ CT or MRI imaging to assess baseline pretreatment or prior to observation
 - ▶ Follow-up imaging every 6–16 weeks as per physician discretion, patient clinical status, and therapeutic schedule. Imaging interval to be adjusted shorter or longer according to rate of disease change and sites of active disease
- Consider MRI (preferred) or CT of head at baseline and as clinically indicated. Annual surveillance scans at physician discretion
- MRI of spine as clinically indicated
- Bone scan as clinically indicated

^c CT is with IV contrast and MRI is with or without contrast.

^d No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on treatment schedules, side effects, comorbidities, and symptoms.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



**FOLLOW-UP
(category 2B)**

Long-Term Follow-Up (>5 years)

- Follow-up should be considered based on assessment of competing sources of mortality, personal risk factors for RCC, patient performance status, and patient preference.
- Follow-up may be performed by a primary care physician if appropriate.
- H&P should be performed annually.
- Laboratory tests should be performed annually in surgical patients to evaluate renal function and determine glomerular filtration rate.
- Imaging:
 - ▶ Abdominal imaging may continue beyond recommended follow-up with increasing intervals given low but significant risk of metachronous tumors and/or late recurrences.
 - ▶ Consider chest imaging for higher stage disease and increasing intervals given low but significant risk of late recurrence.

REFERENCES

Active Surveillance

McIntosh AG, Ristau BT, Ruth K, et al. Active surveillance for localized renal masses: Tumor growth, delayed intervention rates, and >5-yr clinical outcomes. Eur Urol 2018;74:157-164.

Gupta M, Alam R, Patel HD, et al. Use of delayed intervention for small renal masses initially managed with active surveillance. Urol Oncol 2019;37:18-25.

Kassiri B, Cheaib JG, Pierorazio PM. Patients with small renal masses undergoing active surveillance: Is yearly chest imaging necessary? J Urol 2019;201:1061-1063.

Chandrasekar T, Ahmad AE, Fadaak K, et al. Natural history of complex renal cysts: Clinical evidence supporting active surveillance. J Urol 2018;199:633-640.

Jewett MA, Mattar K, Basiuk J, et al. Active surveillance of small renal masses: progression patterns of early stage kidney cancer. Eur Urol 2011;60:39-44.

Ablation

Lay AH, Faddegon S, Olweny EO, et al. Oncologic efficacy of radio frequency ablation for small renal masses: Clear cell vs papillary subtype. J Urol 2015;194:653-657.

Beksac AT, Rivera-Sanfeliz G, Dufour CA, et al. Impact of tumor histology and grade on treatment success of percutaneous renal cryoablation. World J Urol 2017;35:633-640.

Haddad MM, Schmit GD, Kurup AN, et al. Percutaneous cryoablation of solitary, sporadic renal cell carcinoma: Outcome analysis based on clear-cell versus papillary subtypes. J Vasc Interv Radiol 2018;29:1122-1126.

Pierorazio PM, Johnson MH, Patel HD, et al. Management of renal masses and localized renal cancer: Systematic review and meta-analysis. J Urol 2016;196:989-99.

Locally Advanced Disease

Gershman B, Moreira DM, Thompson RH, et al. Renal cell carcinoma with isolated lymph node involvement: Long-term natural history and predictors of oncologic outcomes following surgical resection. Eur Urol 2017;72:300-306.

Long-Term Follow-Up

McIntosh AG, Ristau BT, Ruth K, et al. Active surveillance for localized renal masses: Tumor growth, delayed intervention rates, and >5-yr clinical outcomes. Eur Urol 2018;74:157-164.

Narayan V, Puligandla M, Haas NB, et al. Patterns of relapse and implications for post-nephrectomy surveillance for patients with high-risk non-clear cell renal cell carcinoma: Subgroup analysis of the phase 3 ECOG-ACRIN E2805 trial. J Urol 2019;201:62-68.

Dabestani S, Beisland C, Stewart GD, et al. Long-term outcomes of follow-up for initially localised clear cell renal cell carcinoma: RECUR database analysis. Eur Urol Focus 2019;5:857-866.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2024

Kidney Cancer

NCCN Evidence Blocks™

[NCCN Guidelines Index](#)[Table of Contents](#)[Discussion](#)

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

[See Evidence Blocks on KID-C \(EB-1\)](#)

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

^a [Risk Models to Direct Treatment \(IMDC criteria or MSKCC Prognostic Model\) \(KID-D\)](#).

^b [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

^c Rini BI, et al. Lancet Oncol 2016;17:1317-1324. Harrison MR, et al. Cancer 2021;127:2204-2212. Bex A. Cancer 2021;127:2184-2186.

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

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2024

Kidney Cancer

NCCN Evidence Blocks™

5	E = Efficacy of Regimen/Agent
4	S = Safety of Regimen/Agent
3	Q = Quality of Evidence
2	C = Consistency of Evidence
1	A = Affordability of Regimen/Agent

E S Q C A

[NCCN Guidelines Index](#)[Table of Contents](#)[Discussion](#)

EVIDENCE BLOCKS FOR FIRST-LINE SYSTEMIC THERAPIES FOR CLEAR CELL HISTOLOGY

FAVORABLE-RISK PATIENTS

Preferred Regimens

Axitinib/pembrolizumab



Cabozantinib/nivolumab



Lenvatinib/pembrolizumab



Other Recommended Regimens

Axitinib/avelumab



Cabozantinib



Ipilimumab/nivolumab



Pazopanib



Sunitinib



Useful in Certain Circumstances

Axitinib



High-dose IL-2



POOR/INTERMEDIATE-RISK PATIENTS

Preferred Regimens

Axitinib/pembrolizumab



Cabozantinib/nivolumab



Ipilimumab/nivolumab



Lenvatinib/pembrolizumab



Cabozantinib



Other Recommended Regimens

Axitinib/avelumab



Pazopanib



Sunitinib



Useful in Certain Circumstances

Axitinib



High-dose IL-2



Temirolimus



Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2024

Kidney Cancer

NCCN Evidence Blocks™

[NCCN Guidelines Index](#)[Table of Contents](#)[Discussion](#)

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

[See Evidence Blocks on KID-C \(EB-2\)](#)

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

^b [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

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

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

^f This regimen is for patients that have received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

^g For patients who received ≥2 prior systemic therapies.

^h An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2024

Kidney Cancer

NCCN Evidence Blocks™

5	E = Efficacy of Regimen/Agent
4	S = Safety of Regimen/Agent
3	Q = Quality of Evidence
2	C = Consistency of Evidence
1	A = Affordability of Regimen/Agent

E S Q C A

[NCCN Guidelines Index](#)[Table of Contents](#)[Discussion](#)

EVIDENCE BLOCKS FOR SUBSEQUENT SYSTEMIC THERAPIES FOR CLEAR CELL HISTOLOGY

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY	
IMMUNO-ONCOLOGY (IO) THERAPY HISTORY STATUS	
IO THERAPY NAÏVE	
Other Recommended Regimens	
Axitinib/pembrolizumab	
Cabozantinib	
Cabozantinib/nivolumab	
Ipilimumab/nivolumab	
Lenvatinib/everolimus	
Lenvatinib/pembrolizumab	
Nivolumab	
Useful in Certain Circumstances	
Axitinib	
Everolimus	
Pazopanib	
Sunitinib	
Tivozanib	
Belzutifan	
Bevacizumab	
High-dose IL-2 for selected patients	
Temsirolimus	
Axitinib/avelumab	

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY	
IMMUNO-ONCOLOGY (IO) THERAPY HISTORY STATUS	
PRIOR IO THERAPY	
Other Recommended Regimens	
Axitinib	
Belzutifan	
Cabozantinib	
Lenvatinib/everolimus	
Tivozanib	
Useful in Certain Circumstances	
Axitinib/pembrolizumab	
Cabozantinib/nivolumab	
Everolimus	
Ipilimumab/nivolumab	
Lenvatinib/pembrolizumab	
Pazopanib	
Sunitinib	
Bevacizumab	
High-dose IL-2 for selected patients	
Temsirolimus	
Axitinib/avelumab	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2024

Kidney Cancer

NCCN Evidence Blocks™

[NCCN Guidelines Index](#)[Table of Contents](#)[Discussion](#)

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGYⁱ

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> • Clinical trial • Cabozantinib 	<ul style="list-style-type: none"> • Lenvatinib + everolimus • Nivolumab^b • Nivolumab^b + cabozantinib • Pembrolizumab^b • Sunitinib 	<ul style="list-style-type: none"> • Axitinib • Bevacizumab^h • Bevacizumab^h + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated RCC (HERED-RCC-D) • Bevacizumab^h + everolimus • Erlotinib • Everolimus • Nivolumab^b + ipilimumab^b (category 2B) • Pazopanib • Temsirolimus^e (category 1 for poor-prognosis risk group; category 2A for other risk groups)

[See Evidence Blocks on KID-C \(EB-3\)](#)^b [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).^e The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium >10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, et al. N Engl J Med 2007;356:2271-2281.^h An FDA-approved biosimilar is an appropriate substitute for bevacizumab.ⁱ For collecting duct or medullary subtypes, partial responses have been observed with cytotoxic chemotherapy (carboplatin + gemcitabine, carboplatin + paclitaxel, or cisplatin + gemcitabine) and other platinum-based chemotherapies currently used for urothelial carcinomas. Gemcitabine + doxorubicin can also produce responses in renal medullary carcinoma (RMC) (Wilson NR, et al. Clin Genitourin Cancer 2021;19:e401-e408). Oral targeted therapies generally do not produce responses in patients with RMC; erlotinib + bevacizumab can produce responses even in heavily pretreated patients with RMC. Outside of clinical trials, platinum-based chemotherapy regimens should be the preferred first-line therapy for RMC.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024

Kidney Cancer

NCCN Evidence Blocks™

5	E = Efficacy of Regimen/Agent
4	S = Safety of Regimen/Agent
3	Q = Quality of Evidence
2	C = Consistency of Evidence
1	A = Affordability of Regimen/Agent

E S Q C A

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

EVIDENCE BLOCKS FOR SYSTEMIC THERAPIES FOR NON-CLEAR CELL HISTOLOGY

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY	
Preferred Regimen	
Cabozantinib	
Other Recommended Regimens	
Lenvatinib/everolimus	
Nivolumab	
Nivolumab/cabozantinib	
Pembrolizumab	
Sunitinib	
Useful in Certain Circumstances	
Axitinib	
Bevacizumab	
Bevacizumab/erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated RCC	
Bevacizumab/everolimus	
Erlotinib	
Everolimus	
Nivolumab/ipilimumab	
Pazopanib	
Temsirolimus (poor-prognosis risk)	
Temsirolimus (risk groups other than poor-risk)	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



RISK MODELS TO DIRECT TREATMENT

Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model^a

Prognostic Factors

- Interval from diagnosis to treatment of less than 1 year
- Karnofsky performance status less than 80%
- Serum LDH greater than 1.5 times the upper limit of normal (ULN)
- Corrected serum calcium greater than the ULN
- Serum hemoglobin less than the lower limit of normal (LLN)

Prognostic Risk Groups

- Low-risk group: no prognostic factors
- Intermediate-risk group: one or two prognostic factors
- Poor-risk group: three or more prognostic factors

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria^b

Prognostic Factors

- Less than one year from time of diagnosis to systemic therapy
- Performance status <80% (Karnofsky)
- Hemoglobin < lower limit of normal (Normal: 120 g/L or 12 g/dL)
- Calcium > upper limit of normal (Normal: 8.5–10.2 mg/dL)
- Neutrophil > upper limit of normal (Normal: 2.0–7.0×10⁹/L)
- Platelets > upper limit of normal (Normal: 150,000–400,000)

Prognostic Risk Groups

- Favorable-risk group: no prognostic factors
- Intermediate-risk group: one or two prognostic factors
- Poor-risk group: three to six prognostic factors

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

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2024

Hereditary Renal Cell Carcinoma

NCCN Evidence Blocks™

5	E = Efficacy of Regimen/Agent
4	S = Safety of Regimen/Agent
3	Q = Quality of Evidence
2	C = Consistency of Evidence
1	A = Affordability of Regimen/Agent

E S Q C A

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

CRITERIA FOR FURTHER GENETIC RISK EVALUATION FOR HEREDITARY RCC SYNDROMES^a

1. An individual with a close blood relative^b with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene → [GENE-1](#)
2. An individual with RCC with any of the following criteria:
 - Diagnosed at age ≤46 y^c
 - Bilateral or multifocal tumors
 - ≥1 first- or second-degree relative^b with RCC
3. An individual whose tumors have the following histologic characteristics:
 - Multifocal papillary histology
 - HLRCC-associated RCC, RCC with fumarate hydratase (FH) deficiency or other histologic features associated with HLRCC
 - Birt-Hogg-Dubé syndrome (BHDS)-related histology (multiple chromophobe, oncocytoma, or oncocytic hybrid)
 - Angiomyolipomas of the kidney and one additional tuberous sclerosis complex (TSC) criterion in the same person ([Table 1](#))
 - Succinate dehydrogenase (SDH)-deficient RCC histology^d
4. An unaffected individual^{e,f} with any of the following criteria:
 - ≥2 first- or second-degree relatives^b with RCC (on the same side of the family)
 - Any first-degree relative who meets the criteria in boxes 2 or 3 who is unable or unwilling to genetically test

- Consider referral to cancer genetics professional and Refer to specific syndromes - See [Hereditary RCC Syndromes Overview \(HERED-RCC-2\)](#), See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic: Principles of Cancer Risk Assessment and Counseling ([EVAL-A](#)) and Pedigree ([EVAL-B](#)) → [GENE-1](#)

^a Table adapted from ACMG Practice Guidelines. Hampel H, Bennett RL, Buchanan A, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med 2015;17:70-87. Schuch B, Vourganti S, Ricketts CJ, et al. Defining early-onset kidney cancer: Implications for germline and somatic mutation testing and clinical management. J Clin Oncol 2014;32:431-437.

^b Close blood relatives include the patient's first-degree (ie, parents, siblings, children) and second-degree (ie, half-siblings, aunts, uncles, nieces, nephews, grandparents, grandchildren) relatives.

^c Using age as a sole criterion for genetic risk evaluation is generally not a sensitive method.

^d Tumors that show loss of staining for succinate dehydrogenase complex subunits B (SDHB) have been termed SDH-deficient. Morphology of these tumors may include: solid or focally cystic growth, uniform cytology with eosinophilic flocculent cytoplasm, intracytoplasmic vacuolations and inclusions, and round to oval low-grade nuclei. (Ricketts CJ, Shuch B, Vocke CD, et al. Succinate dehydrogenase kidney cancer: an aggressive example of the Warburg effect in cancer. J Urol 2012;188:2063-2071; Gill AJ, Hes O, Papathomas T, et al. Succinate dehydrogenase [SDH]-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients. Am J Surg Pathol 2014;38:1588-1602; Gill AJ. Succinate dehydrogenase [SDH] and mitochondrial driven neoplasia. Pathology 2012;44:285-292.)

^e If unaffected, when possible, test family member with highest likelihood of a pathogenic/likely pathogenic variant before testing an unaffected individual.

^f Unnecessary in translocational RCC or medullary RCC.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

HERED-RCC-1



NCCN Guidelines Version 2.2024

Hereditary Renal Cell Carcinoma

NCCN Evidence Blocks™

5	E = Efficacy of Regimen/Agent
4	S = Safety of Regimen/Agent
3	Q = Quality of Evidence
2	C = Consistency of Evidence
1	A = Affordability of Regimen/Agent

E S Q C A

[NCCN Guidelines Index](#)[Table of Contents](#)[Discussion](#)

HEREDITARY RCC SYNDROMES OVERVIEW

Syndrome/Gene	Common Histologies	Inheritance Pattern Major Clinical Manifestations	Other Specialists Involved in Screening
von Hippel-Lindau (VHL)/ <i>VHL</i> gene	Clear cell	<ul style="list-style-type: none"> Autosomal dominant Table 2 	<ul style="list-style-type: none"> Neurosurgery Ophthalmology Audiology Endocrinology Endocrine surgery
Hereditary papillary renal carcinoma (HPRC)/ <i>MET</i> gene	Papillary	<ul style="list-style-type: none"> Autosomal dominant Multifocal, bilateral renal cell tumors 	<ul style="list-style-type: none"> Nephrology
Birt-Hogg-Dubé syndrome (BHDS)/ <i>FLCN</i> gene ^{1,2}	Chromophobe, hybrid oncocytic tumors, clear cell, oncocytomas, angiomyolipomas, papillary RCC	<ul style="list-style-type: none"> Autosomal dominant Cutaneous fibrofolliculoma or trichodiscoma, pulmonary cysts, and spontaneous pneumothorax 	<ul style="list-style-type: none"> Pulmonology Dermatology
Tuberous sclerosis complex (TSC)/ <i>TSC1</i> , <i>TSC2</i> genes	Angiomyolipoma (and other PEComas), renal cysts, eosinophilic solid and cystic RCC, RCC with fibromyxomatous stroma, eosinophilic vacuolated tumor, low-grade oncocytic tumor, clear cell	<ul style="list-style-type: none"> Autosomal dominant Table 1 	<ul style="list-style-type: none"> Neurology Dermatology
Hereditary leiomyomatosis and renal cell cancer (HLRCC)/ <i>FH</i> gene	HLRCC associated RCC or FH-deficient RCC	<ul style="list-style-type: none"> Autosomal dominant Leiomyomas of skin and uterus, unilateral, solitary, and aggressive renal cell tumors. PET-positive adrenal adenomas 	<ul style="list-style-type: none"> Gynecology Dermatology
<i>BAP1</i> tumor predisposition syndrome (TPDS)/ <i>BAP1</i> gene ^{3,4}	Clear cell	<ul style="list-style-type: none"> Autosomal dominant Melanoma (uveal and cutaneous), kidney cancer, mesothelioma 	<ul style="list-style-type: none"> Dermatology Ophthalmology Thoracic oncology
Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome/ <i>SDHA/B/C/D</i> genes	SDH-deficient RCC	<ul style="list-style-type: none"> Autosomal dominant Head and neck PGL and adrenal or extra-adrenal PCCs, gastrointestinal stromal tumors (GIST) 	<ul style="list-style-type: none"> Endocrine Endocrine surgery

¹ Schmidt LS, Nickerson ML, Warren MB, et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dubé syndrome. Am J Hum Genet 2005;76:1023-1033.

² Sattler EC, Steinlein OK. Birt-Hogg-Dubé Syndrome. 2006 Feb 27 [Updated 2020 Jan 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.

³ Peña-Llopis S, Vega-Ruweather bín-de-Celis S, Liao A. *BAP1* loss defines a new class of renal cell carcinoma. Nat Genet 2012;44:751-759.

⁴ Hakimi AA, Ostrovnaya I, Reva B. Adverse outcomes in clear cell renal cell carcinoma with mutations of 3p21 epigenetic regulators *BAP1* and *SETD2*: a report by MSKCC and the KIRC TCGA Research Network. Clin Cancer Res 2013;19:3259-3267.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

[See GENE-1](#)

HERED-RCC-2



NCCN Guidelines Version 2.2024

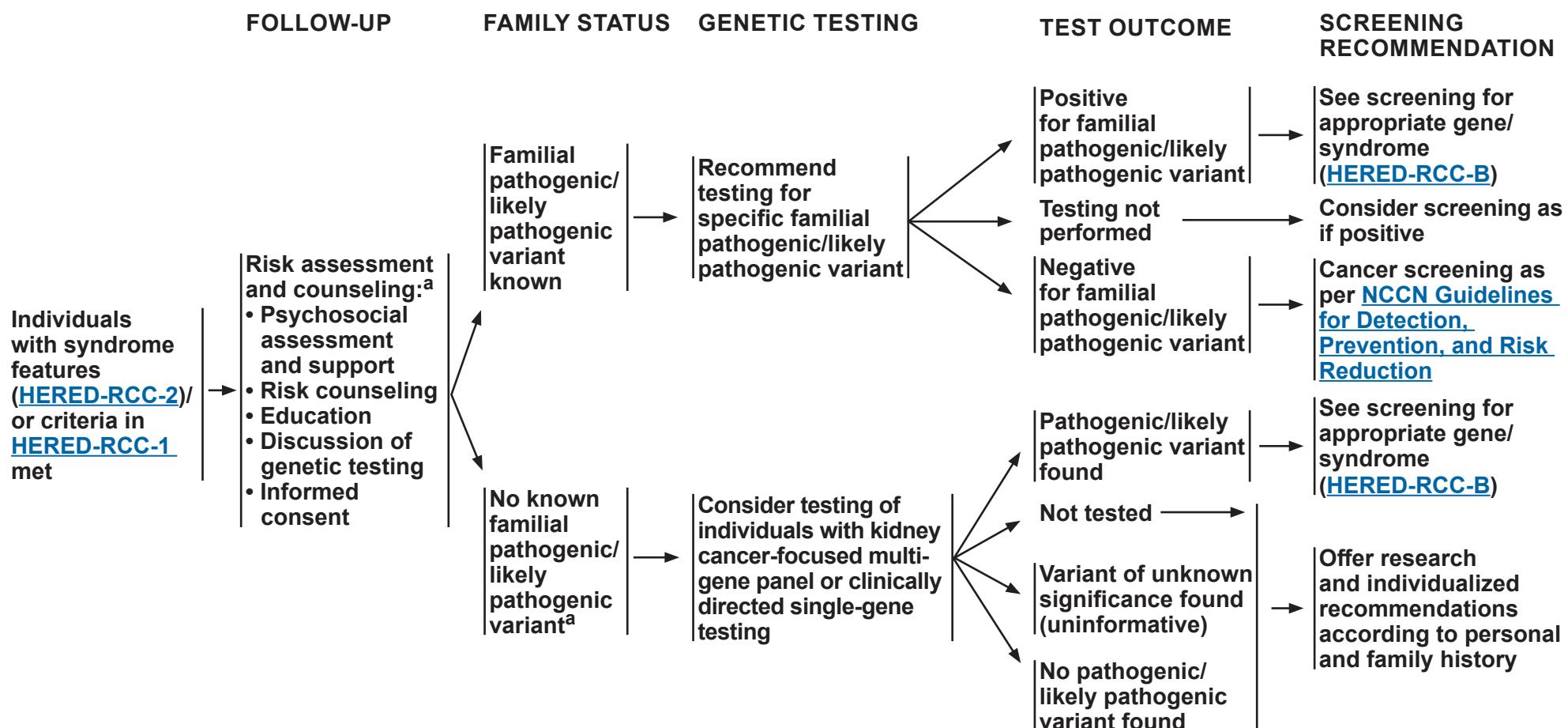
Hereditary Renal Cell Carcinoma

NCCN Evidence Blocks™

5	E = Efficacy of Regimen/Agent
4	S = Safety of Regimen/Agent
3	Q = Quality of Evidence
2	C = Consistency of Evidence
1	A = Affordability of Regimen/Agent

E S Q C A

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)



^a In individuals who meet diagnostic criteria, but in whom no germline mutations are identified, consider workup for mosaicism.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2024

Hereditary Renal Cell Carcinoma

NCCN Evidence Blocks™

5		E = Efficacy of Regimen/Agent
4		S = Safety of Regimen/Agent
3		Q = Quality of Evidence
2		C = Consistency of Evidence
1		A = Affordability of Regimen/Agent

E S Q C A

[NCCN Guidelines Index](#)[Table of Contents](#)[Discussion](#)

Table 1: Features of Tuberous Sclerosis (TSC)

Major Features	Minor Features
<ul style="list-style-type: none"> Renal angiomyolipoma^{a,b} Cardiac rhabdomyoma Cortical dysplasias, including tubers and cerebral white matter migration lines Angiofibromas (≥ 3) or fibrous cephalic plaque Hypomelanotic macules (3 to > 5 mm in diameter) Lymphangioleiomyomatosis (LAM)^a Multiple retinal nodular hamartomas Shagreen patch Subependymal giant cell astrocytoma (SEGA) Subependymal nodules (SENs) Ungual fibromas (≥ 2) 	<ul style="list-style-type: none"> Multiple renal cysts "Confetti" skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs) Dental enamel pits (> 3) Intraoral fibromas (≥ 2) Nonrenal hamartomas Retinal achromic patch

Table 2: Features of Von Hippel-Lindau (VHL) Disease

Major Features	Minor Features
<ul style="list-style-type: none"> Hemangioblastomas of the retina, spine, or brain Clear cell RCC (ccRCC) diagnosed < 40 years of age or multiple/bilateral ccRCC tumors diagnosed at any age Pheochromocytoma (PCCs) PGL of abdomen, thorax, or neck Retinal angiomas 	<ul style="list-style-type: none"> Endolymphatic sac tumors Papillary cystadenomas of the epididymis or broad ligament Pancreatic serous cystadenoma (> 1) Pancreatic neuroendocrine tumor (pNET) or multiple pancreatic cysts (> 1)

^a The combination of angiomyolipoma and LAM does not meet criteria for definite diagnosis.^b Multiple angiomyolipoma are a major feature.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

HERED-RCC-A



NCCN Guidelines Version 2.2024

Hereditary Renal Cell Carcinoma

NCCN Evidence Blocks™

5	E = Efficacy of Regimen/Agent
4	S = Safety of Regimen/Agent
3	Q = Quality of Evidence
2	C = Consistency of Evidence
1	A = Affordability of Regimen/Agent

E S Q C A

[NCCN Guidelines Index](#)[Table of Contents](#)[Discussion](#)

KIDNEY-SPECIFIC SCREENING RECOMMENDATIONS FOR PATIENTS WITH CONFIRMED HEREDITARY RCC WHO DO NOT YET HAVE A RADIOGRAPHIC OR PATHOLOGIC DIAGNOSIS OF RCC

General

- Follow-up should be individualized based on treatment schedules, side effects, comorbidities, and symptoms.
- Whenever possible, screening should be coordinated with another specialist involved in patient's care.
- Patients of childbearing age who are planning conception should consider renal imaging prior to pregnancy.
- If there is a family member with an early diagnosis, screening should begin 10 years before earliest age of diagnosis in family member.
- CT of the abdomen can be used for surgical planning but should be limited if possible for surveillance due to lifetime radiation exposure for hereditary syndromic patients.
- Imaging frequency would be increased once lesions are detected based on growth rate and size of lesion(s).
- For surgical recommendations for each syndrome, see [HERED-RCC-C](#); for systemic therapy, see [HERED-RCC-D](#).

Gene	Screening Recommendations
BAP1-TPDS	• Abdominal MRI (preferred) or CT with and without IV contrast every 2 y starting at age 30 y ¹
BHDS	• Abdominal MRI (preferred) or CT with and without IV contrast every 3 y starting at age 20 y ²
HLRCC	• Abdominal MRI (preferred) or CT with and without IV contrast annually starting at age 8–10 y ³
HPRCC	• Abdominal MRI (preferred) or CT with and without IV contrast every 1–2 y starting at age 30 y ^{4,5}
PGL/PCC	• Abdominal MRI (preferred) or CT with and without IV contrast every 4–6 y starting at age 12 y ^{5,6,8}
TSC	• Abdominal MRI (preferred) or CT with and without IV contrast every 3–5 y starting at age 12 y ⁷
VHL	• Abdominal MRI (preferred) or CT with and without IV contrast to assess kidneys, pancreas, and adrenals every 2 y starting at age 15 y ^{5,9}

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**References on
HERED-RCC-B 2 of 2**

HERED-RCC-B

1 OF 2



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024

Hereditary Renal Cell Carcinoma

NCCN Evidence Blocks™

5	E = Efficacy of Regimen/Agent
4	S = Safety of Regimen/Agent
3	Q = Quality of Evidence
2	C = Consistency of Evidence
1	A = Affordability of Regimen/Agent

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

KIDNEY-SPECIFIC SCREENING RECOMMENDATIONS FOR PATIENTS WITH CONFIRMED HEREDITARY RCC WHO DO NOT YET HAVE A RADIOGRAPHIC OR PATHOLOGIC DIAGNOSIS OF RCC

REFERENCES

- ¹ Star P, Goodwin A, Kapoor R, et al. Germline BAP1-positive patients: the dilemmas of cancer surveillance and a proposed interdisciplinary consensus monitoring strategy. Eur J Cancer 2018;92:48-53.
- ² Menko F, van Steensel M, Giraud S, et al. Birt-Hogg-Dubé syndrome: Diagnosis and management. Lancet Oncol 2009;10:1199-1206.
- ³ Menko F, Maher E, Schmidt L, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): Renal cancer risk, surveillance and treatment. Fam Cancer 2014;13:637-644.
- ⁴ Ornstein DK, Lubensky IA, Venzon D, et al. Prevalence of microscopic tumors in normal appearing renal parenchyma of patients with hereditary papillary renal cancer. J Urol 2000;163:431-433.
- ⁵ Rednam SP, Erez A, Druker H, et al. Von Hippel-Lindau and hereditary pheochromocytoma/paraganglioma syndromes: Clinical features, genetics, and surveillance recommendations in childhood. Clin Cancer Res 2017;23:e68-e75.
- ⁶ Tufton N, Sahdev A, Akker SA. Radiological surveillance screening in asymptomatic succinate dehydrogenase mutation carriers. J Endocr Soc 2017;1:897-907.
- ⁷ Krueger DA, Northrup H; International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013;49:255-265.
- ⁸ Eijkelenkamp K, Osinga TE, de Jong MM, et al. Calculating the optimal surveillance for head and neck paraganglioma in SDHB-mutation carriers. Fam Cancer 2017;16:123-130.
- ⁹ Binderup MLM, Smerdel M, Borgwadt L, et al. von Hippel-Lindau disease: Updated guideline for diagnosis and surveillance. Eur J Med Genet 2022;65:104538.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

HERED-RCC-B
2 OF 2



NCCN Guidelines Version 2.2024

Hereditary Renal Cell Carcinoma

NCCN Evidence Blocks™

5	E = Efficacy of Regimen/Agent
4	S = Safety of Regimen/Agent
3	Q = Quality of Evidence
2	C = Consistency of Evidence
1	A = Affordability of Regimen/Agent

KIDNEY-SPECIFIC SURGICAL RECOMMENDATIONS FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

- Preoperative alert: Patients with a suspected or known diagnosis of PGL/PCC or VHL are at increased risk of PCCs and should have blood and/or urine screening for this prior to any surgical procedure.

BAP1-TPDS

- There are no specific guidelines in surgical management for this syndrome ([KID-A](#)).

BHDS

- Nephron-sparing surgery is the treatment of choice for renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.¹
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

HLRCC

- As these tumors can be aggressive, surveillance of renal tumors is not recommended, and total radical nephrectomy should be considered.²

HPRC

- Nephron-sparing surgery is the treatment of choice for renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

PGL/PCC

- Malignant tumors absent aggressive histology and early stage should undergo surgical resection; partial nephrectomy can be considered.
- For larger tumors and those with aggressive histology (eg, high grade, sarcomatoid), radical nephrectomy should be considered.³

TSC

- Angiomyolipoma is a benign lesion associated with TSC and managed separately.^{4,5,6}
- Nephron-sparing surgery is the treatment of choice for malignant renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.⁷
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

VHL

- Management of localized renal masses in patients with VHL is typically guided under the “3 cm rule.”⁷
- The idea is to intervene at a time point of maximal benefit to the patient to limit the chance of development of metastatic disease but also to consider the recurrent and multiple resections many of these patients will have over the course of their lifetime with subsequent development of chronic and progressive renal failure.^{7,8}
- Patient should undergo partial nephrectomy if at all possible and consider referral to centers with surgical expertise in complex partial nephrectomies and comprehensive care of VHL patients.⁸
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

[References on HERED-RCC-C 2 of 2](#)

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024

Hereditary Renal Cell Carcinoma

NCCN Evidence Blocks™

5		E = Efficacy of Regimen/Agent
4		S = Safety of Regimen/Agent
3		Q = Quality of Evidence
2		C = Consistency of Evidence
1		A = Affordability of Regimen/Agent

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

KIDNEY-SPECIFIC SURGICAL RECOMMENDATIONS FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

REFERENCES

- ¹ Pavlovich CP, Grubb RL 3rd, Hurley K, et al. Evaluation and management of renal tumors in the Birt-Hogg-Dubé syndrome. *J Urol* 2005;173:1482-1486.
- ² Menko FH, Maher ER, Schmidt LS, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. *Fam Cancer* 2014;13:637-644.
- ³ Gill AJ, Hes O, Papathomas T, et al. Succinate dehydrogenase (SDH)-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients. *Am J Surg Pathol* 2014;38:1588-1602.
- ⁴ Krueger DA, Northrup H; International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol* 2013;49:255-265.
- ⁵ Muller A, Rouvire O. Renal artery embolization—indications, technical approaches and outcomes *Nat Rev Nephrol* 2015;11:288-301.
- ⁶ Nelson CP, Sanda MG. Contemporary diagnosis and management of renal angiomyolipoma. *J Urol* 2002;168:1315-1325.
- ⁷ Shuch B, Singer EA, Bratslavsky G. The surgical approach to multifocal renal cancers. *Urol Clin North Am* 2012;39:133-148.
- ⁸ Singer EA, Vourganti S, Lin KY, et al. Outcomes of patients with surgically treated bilateral renal masses and a minimum of 10 years of followup. *J Urol* 2012;188:2084-2088.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

HERED-RCC-C
2 OF 2



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024

Hereditary Renal Cell Carcinoma

NCCN Evidence Blocks™

5	E = Efficacy of Regimen/Agent
4	S = Safety of Regimen/Agent
3	Q = Quality of Evidence
2	C = Consistency of Evidence
1	A = Affordability of Regimen/Agent

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

KIDNEY-SPECIFIC SYSTEMIC THERAPY FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

Syndrome	Kidney-Specific Systemic Therapy
HLRCC	Useful in Certain Circumstances • Erlotinib plus bevacizumab ^{a,b}
TSC	Useful in Certain Circumstances • Everolimus ^c
VHL	Preferred Regimen • Belzutifan ^{d,e} Useful in Certain Circumstances • Pazopanib ^f

[See Evidence Blocks on HRCC-D \(EB-1\)](#)

^a An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

^b There are no specific FDA-approved therapies for HLRCC. Treatment with erlotinib plus bevacizumab demonstrated benefit in patients with metastatic RCC from HLRCC. Srinivasan R, Gurram S, Al Harthy M, et al. Results from a phase II study of bevacizumab and erlotinib in subjects with advanced hereditary leiomyomatosis and renal cell cancer (HLRCC) or sporadic papillary renal cell cancer [abstract]. J Clin Oncol 2020;38:(15_suppl) 5004-5004.

^c Everolimus is an FDA-approved therapy for asymptomatic, growing angiomyolipoma measuring >3 cm in diameter. Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2013;381:817-824.

^d Belzutifan is FDA-approved for the treatment of VHL-associated-RCC, central nervous system (CNS) hemangioblastomas, or pNET, not requiring immediate surgery.

^e Jonasch E, Donskov F, Iliopoulos O, et al. Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease. N Engl J Med 2021;385:2036-2046.

^f Pazopanib was associated with a >50% objective response rate in renal lesions in a 31-patient phase II study. Jonasch E, McCutcheon IE, Gombos DS, et al. Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-centre, phase 2 trial. Lancet Oncol 2018;19:1351-1359.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

HERED-RCC-D



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024

Hereditary Renal Cell Carcinoma

NCCN Evidence Blocks™

5	E = Efficacy of Regimen/Agent
4	S = Safety of Regimen/Agent
3	Q = Quality of Evidence
2	C = Consistency of Evidence
1	A = Affordability of Regimen/Agent

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

EVIDENCE BLOCKS FOR KIDNEY-SPECIFIC SYSTEMIC THERAPY FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

HLRCC	
Useful in Certain Circumstances	
Erlotinib/bevacizumab	
TSC	
Useful in Certain Circumstances	
Everolimus	
VHL	
Preferred Regimen	
Belzutifan	
Useful in Certain Circumstances	
Pazopanib	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2024

Kidney Cancer

NCCN Evidence Blocks™

**Table 1. American Joint Committee on Cancer (AJCC)
TNM Staging System for Kidney Cancer (8th ed., 2017)**

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumor >4 cm but ≤7 cm in greatest dimension, limited to the kidney
T2	Tumor >7 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney
T2b	Tumor >10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor extends into the vena cava below the diaphragm
T3c	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Used with the permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Table 2. AJCC Prognostic Groups

	T	N	M
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1-T2	N1	M0
	T3	NX,N0-N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

Table 3. Histologic Grade (G)

GX	Grade cannot be assessed
G1	Nucleoli absent or inconspicuous and basophilic at 400x magnification
G2	Nucleoli conspicuous and eosinophilic at 400x magnification, visible but not prominent at 100x magnification
G3	Nucleoli conspicuous and eosinophilic at 100x magnification
G4	Marked nuclear pleomorphism and/or multinucleate giant cells and/or rhabdoid and/or sarcomatoid differentiation



ABBREVIATIONS

ARCC	advanced renal cell carcinoma	IMDC	International Metastatic Renal Cell Carcinoma Database Consortium	SBRT	stereotactic body radiation therapy
BHDS	Birt-Hogg-Dubé syndrome	IL-2	interleukin-2	SEGA	subependymal giant cell astrocytoma
CBC	complete blood count	IO	Immuno-oncology	SENs	subependymal nodules
ccRCC	clear cell renal cell carcinoma	LAM	lymphangioleiomyomatosis	TPDS	tumor predisposition syndrome
ECOG	Eastern Cooperative Oncology Group	LLN	lower limit of normal	TSC	tuberous sclerosis complex
FDG	F-18 fluorodeoxyglucose	PCC	pheochromocytoma	ULN	upper limit of normal
FNA	fine-needle aspiration	PGL	paraganglioma	VHL	von Hippel-Lindau
GIST	gastrointestinal stromal tumor	pNET	pancreatic neuroendocrine tumor		
H&P	history and physical	PS	performance status		
HLRCC	hereditary leiomyomatosis and renal cell cancer	RANK	receptor activator of nuclear factor k B		
HPRC	hereditary papillary renal carcinoma	RCC	renal cell carcinoma		



NCCN Categories of Evidence and Consensus

- | | |
|--------------------|--|
| Category 1 | Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| Category 2A | Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| Category 2B | Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. |
| Category 3 | Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. |

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference

- | | |
|--|---|
| Preferred intervention | Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability. |
| Other recommended intervention | Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes. |
| Useful in certain circumstances | Other interventions that may be used for selected patient populations (defined with recommendation). |

All recommendations are considered appropriate.



NCCN Guidelines Version 2.2024

Kidney Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Kidney Cancer. Last updated: January 17th, 2023.

Table of Contents

Overview.....	MS-2
Guidelines Update Methodology	MS-2
Literature Search Criteria.....	MS-2
Sensitive/Inclusive Language Usage	MS-3
Initial Evaluation and Staging	MS-3
Treatment of Localized Disease.....	MS-4
Management of Stage I (T1a) Disease	MS-5
Management of Stage I (T1b) Disease	MS-6
Management of Stage II and III Disease	MS-6
Follow-up After Treatment of Localized Disease.....	MS-7
Management of Relapsed or Stage IV Disease.....	MS-9
Prognostic Models for Metastatic Disease	MS-9
Surgical Options for Patients with Relapsed or Stage IV Disease.....	MS-10
Systemic Therapy Options for Patients with Relapsed or Stage IV Disease	MS-11
First-Line Systemic Therapy Options for Patients with Clear Cell RCC (ccRCC).....	MS-12
Subsequent Systemic Therapy Options for Patients with Clear Cell RCC (ccRCC).....	MS-15
Systemic Therapy for Patients with Non-Clear Cell RCC (nccRCC)	MS-19

Follow-up Recommendations for Relapsed or Stage IV Disease and Surgically Unresectable Disease MS-22

Supportive Care..... MS-23

Hereditary RCC Syndromes..... MS-23

 Genetic Testing and Surveillance Recommendations for Individuals with a Personal or Family History of an RCC Syndrome

 Genetic Testing and Screening Recommendations for Patients with a Clinical Diagnosis of RCC Who Have Characteristics Consistent with Inherited RCC

Kidney-Specific Surgical Recommendations for Patients with a Confirmed Hereditary RCC Syndrome

Kidney-Specific Systemic Therapy for Patients with Confirmed Hereditary RCC

Data Summary..... MS-26

Table 1: Key Studies on First-Line Therapy for Patients with Clear Cell RCC (ccRCC)..... MS-27

Table 2: Key Studies on Subsequent Therapy for Patients with Clear Cell RCC (ccRCC)..... MS-31

Table 3: Key Studies on Systemic Therapy for Patients with Non-Clear Cell RCC (nccRCC)..... MS-34



NCCN Guidelines Version 2.2024

Kidney Cancer

Overview

An estimated 79,000 Americans will be diagnosed with cancers of the kidney and renal pelvis and 13,920 will die of the disease in the United States in 2022.^{1,2} Renal cell carcinoma (RCC) comprises approximately 4.1% of all new cancers, with a median age at diagnosis of 64 years.³ Approximately 85% of kidney tumors are RCC, and approximately 70% of these have a clear cell histology (ccRCC).⁴⁻⁶ Other less common cell types include papillary, chromophobe, translocation, and Bellini duct (collecting duct) tumors.⁷ Medullary renal carcinoma is a rare and aggressive RCC variant that almost exclusively arises in patients who are sickle-cell trait positive.⁸ The histologic diagnosis of RCC is established after surgical removal of renal tumors or after biopsy.

Smoking, obesity, and hypertension are established risk factors for RCC development. Several hereditary types of RCC also exist, with von Hippel-Lindau (VHL) disease being the most common. VHL disease is caused by an autosomal-dominant constitutional mutation in the *VHL* gene that predisposes to ccRCC and other proliferative vascular lesions.⁹⁻¹² (Also see *Hereditary RCC Syndromes* in this Discussion.)

Analysis of the SEER database indicates that RCC incidence has been rising on average 0.6% each year and death rates have been falling on average 1.6% each year from 2010 through 2019.³ The 5-year survival rate for localized RCC has increased from 88.4% (during 1992–1995) to 93.0% (during 2012–2018) and for advanced disease from 7.3% (during 1992–1995) to 15% (during 2012–2018).¹³ The most important prognostic determinants of 5-year survival are the tumor stage, grade, local extent of the tumor, presence of regional nodal metastases, and evidence of metastatic disease at presentation.¹⁴⁻²³ RCC primarily metastasizes to the lung, bone, liver, lymph nodes, adrenal gland, and brain.^{10,24,25}

The NCCN Guidelines for Kidney Cancer provide multidisciplinary recommendations for the clinical management of patients with ccRCC and non-clear cell RCC (nccRCC). These NCCN Guidelines are intended to assist with clinical decision-making, but they cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Medical practitioners should note that unusual patient scenarios (presenting in <5% of patients) are not specifically discussed in these guidelines.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of this version of the NCCN Guidelines® for Kidney Cancer, an electronic search of the PubMed database was performed to obtain key literature on Kidney Cancer published since the previous Guidelines update, using the following search terms: Renal Cell Carcinoma or Kidney Cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence



NCCN Guidelines Version 2.2024

Kidney Cancer

is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Initial Evaluation and Staging

Patients with RCC typically present with a suspicious mass involving the kidney that has been visualized using a radiographic study, often a CT scan. As the use of imaging methods (eg, abdominal CT with or without pelvic CT, MRI) has become more widespread, the frequency of incidental detection of RCC has increased,^{26,27} and fewer patients present with the typical triad symptoms (hematuria, flank mass, and flank pain).

Less frequently, patients present with signs or symptoms resulting from metastatic disease, including bone pain, adenopathy, and pulmonary symptoms attributable to lung parenchyma or mediastinal metastases. Other presentations include fever, weight loss, anemia, or a varicocele.

RCC in younger patients (≤ 46 years) may indicate an inheritable disorder,²⁸ and these patients should be referred to a hereditary cancer clinic for further evaluation.

A thorough physical examination should be performed along with obtaining a complete medical history of the patient. Laboratory evaluation includes a complete blood count (CBC), comprehensive metabolic panel, and lactate dehydrogenase (LDH). The metabolic panel may include serum corrected calcium, serum creatinine, liver function studies, and urinalysis.

CT of the abdomen with or without pelvic CT and CT chest (preferred) or chest x-ray are essential studies in the initial workup.^{29,30,31} Abdominal MRI is used to evaluate the inferior vena cava if tumor involvement is suspected, or it can be used instead of CT for detecting renal masses and for staging when contrast material cannot be administered because of allergy or moderate renal insufficiency.^{32,33} All imaging studies should be performed with and without contrast, such as renal protocol.

A central renal mass may suggest the presence of urothelial carcinoma; if so, urine cytology, ureteroscopy, or percutaneous mass biopsy (if metastatic disease is present or the patient cannot tolerate ureteroscopy) should be considered.

Most bone and brain metastases are symptomatic at diagnosis. Therefore, a bone scan is not routinely performed unless the patient has an elevated serum alkaline phosphatase (ALP) or complains of bone pain.³⁴ MRI of the brain can be performed if clinical signs, presentation, and symptoms suggest brain metastases.



NCCN Guidelines Version 2.2024

Kidney Cancer

The recommended abdominal imaging studies provide high diagnostic accuracy. Therefore, a needle biopsy is not always necessary before surgery, especially in patients whose results show clear findings in the imaging studies. In selected individuals, needle biopsy may be considered for small lesions to establish the diagnosis of RCC and guide active surveillance strategies, cryosurgery, radiofrequency, and ablation strategies.³⁵ As noted above, biopsy should also be considered if a central lesion or a homogeneous infiltration of renal parenchyma is observed on scans to rule out urothelial carcinoma or lymphoma, respectively.

The value of PET in RCC remains to be determined. Currently, PET or PET/CT is not an imaging tool that is recommended to diagnose kidney cancer or to follow for evidence of relapse after nephrectomy.³⁶

If patients present with multiple renal masses, are 46 years old or younger at diagnosis, or have a family history of RCC, they should consider genetic evaluation (see *Hereditary RCC Syndromes* in this Discussion).

Treatment of Localized Disease

Surgical resection remains an effective therapy for clinically localized RCC, with options including radical nephrectomy and nephron-sparing surgery—each detailed below. Each of these modalities is associated with its benefits and risks, the balance of which should optimize long-term renal function and expected cancer-free survival.

Nephron-Sparing Surgery and Radical Nephrectomy

A radical nephrectomy includes a perifascial resection of the kidney, perirenal fat, regional lymph nodes, and ipsilateral adrenal gland. Radical nephrectomy is the preferred treatment if the tumor extends into the inferior vena cava. Open, laparoscopic, or robotic surgical techniques may be used to perform radical nephrectomy. Long-term outcomes data indicate that laparoscopic and open radical nephrectomies have equivalent cancer-free survival rates.³⁷⁻⁴⁴

Originally, partial nephrectomy (nephron-sparing surgery) was indicated only in clinical settings in which a radical nephrectomy would render the patient functionally anephric, necessitating dialysis. These settings include RCC in a solitary kidney, RCC in one kidney with inadequate contralateral renal function, and bilateral synchronous RCC.

Partial nephrectomy has well-established oncologic outcomes data comparable to radical nephrectomy.⁴⁵⁻⁵⁰ Radical nephrectomy can lead to an increased risk for chronic kidney disease^{51,52} and is associated with increased risks of cardiovascular morbidity and mortality according to population-based studies.⁵³ When compared with radical nephrectomy, partial nephrectomy can achieve preserved renal function, decreased overall mortality, and reduced frequency of cardiovascular events.⁵³⁻⁵⁷ Patients with a hereditary form of RCC, such as VHL disease, should also be considered for nephron-sparing therapy. Nephron-sparing surgery has been used increasingly in patients with T1a and T1b renal tumors (ie, ≤7 cm in greatest dimension) and a normal contralateral kidney, with equivalent outcomes to radical nephrectomy.^{48,58-60} Radical nephrectomy should not be employed when nephron sparing can be achieved. A more recent study showed that among Medicare beneficiaries with early-stage kidney cancer, treatment with partial rather than radical nephrectomy was associated with improved survival.⁶¹

Studies with limited follow-up data show that the oncologic outcome for laparoscopic versus open nephron-sparing surgery appears to be similar.^{62,63} A study of oncologic outcomes at 7 years after surgery found metastasis-free survival to be 97.5% and 97.3% ($P = .47$) after laparoscopic and open nephron-sparing surgery, respectively.⁶⁴

The goals of nephron-sparing surgery should be obtaining optimal locoregional tumor control while minimizing ischemia time to ideally less than 30 minutes.⁶⁵ However, in some patients with localized RCC, nephron-sparing surgery may not be suitable because of locally advanced



NCCN Guidelines Version 2.2024

Kidney Cancer

tumor growth or because the tumor is in an unfavorable location. Laparoscopic, robotic, and open partial nephrectomy all offer comparable outcomes in the hands of skilled surgeons. Patients in satisfactory medical condition should undergo surgical excision of stage I through III tumors.

Lymph Node Dissection

Lymph node dissection has not been consistently shown to provide therapeutic benefit. The EORTC phase III trial compared radical nephrectomy with a complete lymph node dissection to radical nephrectomy alone. The results showed no significant differences in overall survival (OS), time to progression of the disease, or progression-free survival (PFS) between the two study groups.⁶⁶ However, primary tumor pathologic features such as nuclear grade, sarcomatoid component, tumor size, stage, and presence of tumor necrosis were all factors that influenced the likelihood of regional lymph node involvement at the time of radical nephrectomy.⁶⁷ Assessment of lymph node status is based on enlargement of imaging (CT/MRI) and on assessment by direct palpation at the time of surgery. CT/MRI may not detect small metastases in normal lymph nodes.⁶⁸ A systematic review and meta-analysis reported that nephrectomy with routine lymph node dissection did not show any OS and PFS benefit for non-metastatic RCC patients and had negative effects on cancer-specific survival.⁶⁹

The NCCN Kidney Cancer Panel recommends regional lymph node dissection for patients with palpable or enlarged lymph nodes detected on preoperative imaging tests.

Adrenalectomy

Ipsilateral adrenal gland resection should be considered for patients with large upper pole tumors or abnormal-appearing adrenal glands on CT.⁷⁰⁻⁷² Adrenalectomy is not indicated when imaging shows a normal adrenal gland or if the tumor is not high risk, based on size and location.⁷³

Active Surveillance and Ablative Techniques

Active surveillance^{74,75} is defined as the initial monitoring of tumors using abdominal imaging techniques with delayed intervention when indicated. Elderly patients and those with small renal masses (<2 cm) and other comorbidities often have low RCC-specific mortality.⁷⁶ Active surveillance and ablative techniques such as cryotherapy or radiofrequency ablation are alternative strategies for selected patients, particularly the elderly and those with competing health risks. Stereotactic body radiation therapy (SBRT) may be considered for medically inoperable patients with stage I kidney cancer (category 2B) and with stage II/III kidney cancer (category 3 for both).

Randomized phase III comparison of ablative techniques with surgical resection (ie, radical or partial nephrectomy by open or laparoscopic techniques) has not been performed.

The NCCN Kidney Cancer Panel has addressed the utility of each of the above-mentioned treatment modalities for localized disease in the context of tumor stages: stage I (T1a and T1b), stage II, and stage III.

Management of Stage I (T1a) Disease

The panel prefers surgical excision by partial nephrectomy for the management of clinical stage I (T1a) renal masses. Adequate expertise and careful patient selection are important. Partial nephrectomy is most appropriate in patients with small unilateral stage I–III tumors or whenever preservation of renal function is a primary issue, such as in patients having one kidney or those with renal insufficiency, bilateral renal masses, or familial RCC. Partial nephrectomy is also appropriate for patients at relative risk for developing progressive chronic kidney disease due to young age or medical risk factors (eg, hypertension, diabetes, nephrolithiasis). Both open and laparoscopic approaches to partial



NCCN Guidelines Version 2.2024

Kidney Cancer

nephrectomy can be considered, depending on tumor size, location, and the surgeon's expertise.

Some localized renal tumors may not be amenable to partial nephrectomy, in which case radical nephrectomy is recommended. The NCCN Guidelines also list radical nephrectomy as an alternative for patients with stage I (T1a) RCC if a partial nephrectomy is not technically feasible as determined by the urologic surgeon.

Other options in selected patients with stage I (T1a) RCC include active surveillance and ablative techniques. Active surveillance is an option for the management of localized renal masses and should be a primary consideration for patients with decreased life expectancy or extensive comorbidities that would place them at excessive risk for more invasive intervention. Short- and intermediate-term oncologic outcomes indicate that an appropriate strategy is to initially monitor small renal masses, and, if required, treat for progression.⁷⁴

Although distant recurrence-free survival rates of ablative techniques and conventional surgery are comparable, ablative techniques may require multiple treatments to achieve the same local oncologic outcomes as conventional surgery.^{77,78} Recent meta-analysis of 32 observational studies and 1 randomized controlled trial (RCT) concluded that ablative therapy in T1a patients resulted in worse OS (hazard ratio [HR], 1.64; 95% CI, 1.39–1.95) as compared to partial nephrectomy but resulted in similar local recurrence-free survival (HR, 1.54; 95% CI, 0.88–2.71) and a smaller decline in estimated glomerular filtration rate postoperatively (MD: -7.42, 95% CI, -13.1 to -1.70). Oncologic outcomes in T1b patients showed some potential benefit, although more clinical evidence in this regard is lacking.⁷⁹ Judicious patient selection and counseling remain of paramount importance for these less invasive technologies. The NCCN Guidelines recommend ablative techniques only in patients with stage I (T1a) RCC.

Management of Stage I (T1b) Disease

Partial nephrectomy for localized RCC has an oncologic outcome similar to that of radical surgery for T1b tumors.^{80,81} Surgery by partial nephrectomy, whenever feasible, or by radical nephrectomy is the standard of care for clinical T1b tumors according to the NCCN Kidney Cancer Panel. Select patients may be managed by active surveillance.

Management of Stage II and III Disease

The curative therapy for patients with stages II and III disease remains radical nephrectomy.⁴³ Radical nephrectomy is the preferred treatment for tumors that extend into the inferior vena cava. Resection of a caval or atrial thrombus often requires the assistance of cardiovascular surgeons because treatment-related mortality may reach 10%, depending on the local extent of the primary tumor and the level of vena caval extension. Partial nephrectomy is generally not suitable for patients with locally advanced tumors; however, it may be performed in patients with locally advanced tumors if technically feasible and clinically indicated. For example, partial nephrectomy may be considered for those with small, polar, unilateral tumors.

The panel lists radical nephrectomy or partial nephrectomy, if feasible or indicated, as options for stage II and III tumors.

Adjuvant Treatment for Clear Cell, High-Risk Localized RCC

For most patients with localized RCC, the benefits of adjuvant treatment after nephrectomy in patients who have undergone a complete resection of their tumor are not yet clearly established. Adjuvant radiation therapy after nephrectomy has not shown benefit, even in patients with nodal involvement or incomplete tumor resection.

Over the years, several vascular endothelial growth factor (VEGF) receptor targeted tyrosine kinase inhibitors (TKIs) have been evaluated in



NCCN Guidelines Version 2.2024 Kidney Cancer

the adjuvant setting with contrasting results. The phase III ASSURE trial compared the use of adjuvant TKIs (sorafenib or sunitinib) for one year with placebo in locally advanced non-metastatic RCC patients with clear or non-clear histology, following nephrectomy.⁸² The trial showed no improvement in disease-free survival (DFS) and OS in TKI-treated patients versus placebo, with high rates of adverse events (AEs) reported. The PROTECT trial evaluating the use of pazopanib versus placebo as an adjuvant treatment for high-risk patients with ccRCC also failed to demonstrate a DFS or OS benefit and reported high toxicity.⁸³ The ATLAS trial evaluating axitinib in the adjuvant setting also did not demonstrate a DFS benefit.⁸⁴

The phase III S-TRAC trial was the first to show benefits in DFS with sunitinib adjuvant treatment following nephrectomy in patients of RCC with clear cell histology. S-TRAC was a multicenter, randomized study including 615 patients with locoregional, high-risk ccRCC treated with adjuvant sunitinib or placebo. Patients treated with sunitinib had a longer median DFS duration compared to those treated with placebo (6.8 years vs. 5.6 years; $P = .03$). Grade 3 or higher AEs occurred in 63.4% of patients treated with sunitinib compared to 21.7% of those on placebo.^{85,86} Median OS had not been reached in the sunitinib or placebo groups in either of these publications.^{85,86} Two recent meta-analyses of five RCTs evaluating adjuvant TKI monotherapies also concluded that they offer no benefit in OS or DFS and have significantly higher AE risks.^{87,88}

Concerns about toxicity, lack of a demonstrated OS benefit, and conflicting results between the S-TRAC trial and the ASSURE/ATLAS/PROTECT trials led to a category 3 recommendation for the use of adjuvant sunitinib for patients with stage III disease, clear cell histology, and a high risk for relapse.

Immune checkpoint inhibitors (ICIs) that target programmed death receptor-1 (PD-1) on T cells have also been investigated in the adjuvant

setting. The phase III multicenter, randomized, double-blind, placebo-controlled KEYNOTE-564 trial investigated the use of pembrolizumab versus placebo in 994 patients with locoregional RCC with a clear-cell histology and an intermediate-to-high or high risk of recurrence (ie, tumor stage 2 with nuclear grade 4 or sarcomatoid differentiation, tumor stage 3 or higher, regional lymph node metastasis) after nephrectomy, or stage M1 with NED (no evidence of disease) status after nephrectomy and resection of metastatic lesions.⁸⁹ DFS was noted in 77.3% of patients treated with pembrolizumab as compared to 68.1% of patients given placebo at 24 months (HR for recurrence or death, 0.68; 95% CI, 0.53–0.87; $P = .002$). OS at 24 months was estimated to be 96.6% in pembrolizumab-treated patients versus 93.5% in the placebo group. Grade 3 or higher AEs occurred in 32.4% of pembrolizumab-treated patients versus 17.7% of those who received placebo.⁸⁹

Based on the KEYNOTE-564 trial results, the panel recommends including pembrolizumab as an adjuvant treatment for patients with stage 2 RCC with grade 4 or sarcomatoid features and clear cell histology as well as for stage 3 ccRCC patients. The panel also recommends adjuvant pembrolizumab for treatment of stage 4 ccRCC after metastasectomy with complete resection of disease, within a year of nephrectomy. Due to the lack of evidence on the role of adjuvant pembrolizumab therapy for patients with RCC with non-clear cell histology, the panel does not recommend including it as a treatment option for non-clear cell histology.

Follow-up After Treatment of Localized Disease

After surgical excision, 20% to 30% of patients with localized tumors experience relapse. Lung metastasis is the most common site of distant recurrence, occurring in 50% to 60% of patients. The median time to relapse after surgery is 1 to 2 years, with most relapses occurring within 3 years.⁹⁰



NCCN Guidelines Version 2.2024

Kidney Cancer

The panel has provided a framework for follow-up of patients undergoing surveillance of a small renal mass and for patients who underwent surgery or ablative therapy for primary RCC. The panel has reiterated in a footnote that no single follow-up plan is appropriate for everyone, and follow-up should be modified for the individual patient using clinical judgment. Since uniform consensus among the panel members regarding the most appropriate follow-up plan is lacking, these recommendations are listed as category 2B. Also, the guidance for follow-up has been provided for the first 5 years after nephrectomy, with follow-up evaluation to be extended beyond 5 years at the discretion of the physician. Results from a retrospective analysis indicate that in a subset of patients, relapses occur more than 5 years after surgery for their primary RCC.⁹¹ The analysis suggests that continued follow-up/surveillance after 5 years may be of potential value in some patients. Another retrospective analysis suggests that patients with lower risk are more likely to relapse later.⁹² Identification of subsets of patients with higher risk who require longer follow-up has not been defined, and further research is required to refine follow-up strategies for patients with RCC.

The NCCN Guidelines incorporate a risk-stratified use of imaging that may target those patients most in need of intensive surveillance and/or imaging tests during follow-up.

Follow-up During Active Surveillance for Stage T1a

For follow-up during active surveillance, the panel recommends an annual history and physical examination and annual laboratory tests as clinically indicated. In order to study the growth rate of the tumor, the panel recommends abdominal imaging (CT or MRI with contrast) within 6 months from initiation of active surveillance; subsequent imaging (with CT, MRI, or ultrasound [US]) may be performed annually thereafter. All three modalities (US, CT, and MRI) have been found to accurately predict pathologic tumor size in a retrospective analysis.⁹³ Therefore, best clinical

judgment should be used in choosing the imaging modality. The panel recommends chest x-ray or chest CT at baseline and annually as clinically indicated to assess for pulmonary metastases. Repeat chest imaging can be considered if intervention is being contemplated. The panel notes that follow-up may be individualized based on surgical status, treatment schedules, side effects, comorbidities, and symptoms.

Follow-up After Ablative Therapy for Stage T1a

Most follow-up tests after ablative therapy included by the panel are similar to those recommended during active surveillance. For imaging, the panel recommends abdominal CT or MRI with and without IV contrast (unless otherwise contraindicated) at 1 through 6 months to assess treatment response, followed by annual abdominal CT or MRI (preferred) for 5 years or longer as clinically indicated. If the patient cannot receive IV contrast, MRI is preferred. If imaging results or clinical findings suggest recurrence, then more frequent imaging, biopsy, or further treatment may be indicated.

For those who have biopsy-proven low-risk pathologic features (no sarcomatoid, low-grade [grade 1/2] RCC, non-diagnostic biopsies, or no prior biopsy, the panel also recommends annual chest x-ray or CT for 5 years to assess for pulmonary metastases.

Follow-up After Partial or Radical Nephrectomy for Stages I–II

For patients with stage I or II RCC, who underwent a partial or radical nephrectomy, the panel recommends an annual history and physical examination and annual laboratory tests as clinically indicated. For patients with stage I RCC, the panel recommends a baseline abdominal CT or MRI (preferred) within 3 to 12 months following renal surgery, then annually for up to 5 years or longer as clinically indicated. For patients with stage II RCC, the panel recommends an increase in abdominal imaging frequency, with baseline abdominal CT or MRI (preferred) every 6 months for 2 years, then annually for up to 5 years or longer as clinically indicated.



NCCN Guidelines Version 2.2024

Kidney Cancer

A more rigorous imaging schedule can be considered if the patient has positive margins or adverse pathologic features (eg, sarcomatoid, grade 3/4 RCC). The rates of local recurrence for smaller tumors after partial nephrectomy are 1.4% to 2% versus 10% for larger tumors.^{62,94,95} The panel also recommends yearly chest x-ray or CT for at least 5 years and as clinically indicated thereafter. As mentioned above, a more rigorous imaging schedule (CT preferred) can be considered if the patient has positive margins or adverse pathologic features.

Follow-up for Patients with Stage III RCC

For patients with stage III RCC, larger tumors have a substantially higher risk of both local and metastatic recurrence, which warrants an increased follow-up frequency compared with patients with stage I or II RCC. Therefore, for these patients, the panel recommends a history and physical examination every 3 to 6 months for 3 years, then annually for up to 5 years. The follow-up evaluation may be extended beyond 5 years at the discretion of the physician as clinically indicated. Comprehensive metabolic panel and other tests are recommended as indicated every 3 to 6 months for 3 years, then annually up to 5 years, and as clinically indicated thereafter.

The panel recommends baseline abdominal CT or MRI within 3 to 6 months following surgery, followed by CT, MRI (preferred), or US every 3 to 6 months for at least 3 years, and annually thereafter for up to 5 years. There is disagreement among the panel members regarding the usefulness of US in patients with stage III disease; therefore, it is listed as a category 2B option specifically for patients with stage II disease.

The panel also recommends baseline chest CT within 3 to 6 months following surgery, followed by continued imaging (CT preferred) every 3 to 6 months for at least 3 years, and annually thereafter for up to 5 years.

While the use of US imaging for follow-up is an option for low-risk patients, CT is the preferred modality for those with a high risk of recurrence. The panel notes that imaging beyond 5 years may be performed as clinically indicated, and additional site-specific imaging (eg, bone scan, brain imaging) may be performed as symptoms warrant.

Alternate surveillance programs have been proposed, such as the surveillance protocol based on the University of California Los Angeles (UCLA) Integrated Staging System (UISS).⁹⁶ The UISS is an evidence-based system in which patients are stratified based on the 1997 TNM (tumor, node, metastasis) stage, grade, and ECOG performance status into low-, intermediate-, or high-risk groups for developing recurrence or metastases for post-surgical treatment of localized or locally advanced RCC.⁹⁶

Management of Relapsed or Stage IV Disease

Prognostic Models for Metastatic Disease

Prognostic scoring systems have been developed to define risk groups of patients by combining independent prognostic factors for survival in patients with metastatic RCC.^{97,98}

The first prognostic factor model to be widely applied was from the Memorial Sloan Kettering Cancer Center (MSKCC). The model was derived from examining prognostic factors in patients ($n = 463$) with metastatic RCC enrolled in clinical trials and treated with interferon (IFN).⁹⁷ Prognostic factors for multivariable analysis included five variables: interval from diagnosis to treatment of less than 1 year; Karnofsky Performance Status (KPS) less than 80%; serum LDH greater than 1.5 times the upper limit of normal (ULN); corrected serum calcium greater than the ULN; and serum hemoglobin less than the lower limit of normal (LLN). Patients with none of these factors are considered low risk or with good prognosis, those with one or two factors present are considered an



NCCN Guidelines Version 2.2024 Kidney Cancer

intermediate risk, and patients with three or more of the factors are considered poor risk. The MSKCC criteria have been additionally validated by an independent group at the Cleveland Clinic.⁹⁹

A prognostic model derived from a population of patients with metastatic RCC treated with VEGF-targeted therapy followed the IMDC (International Metastatic RCC Database Consortium) model.⁹⁸ This model was derived from a retrospective study of 645 patients with metastatic RCC treated with sunitinib, sorafenib, or bevacizumab plus IFN. Patients who received prior immunotherapy (ie, received their targeted therapy as second-line treatment) also were included in the analysis. The analysis identified six clinical parameters to stratify patients into favorable, intermediate, and poor prognosis groups. Four of the five adverse prognostic factors are those previously identified by MSKCC as independent predictors of short survival: hemoglobin less than the LLN, serum-corrected calcium greater than the ULN, KPS less than 80%, and time from the initial diagnosis to initiation of therapy of less than 1 year. Additional, independent, adverse prognostic factors validated in this model are absolute neutrophil count (ANC) greater than ULN and platelets greater than ULN.⁹⁸

Patients with none of the identified six adverse factors were in the favorable-risk category ($n = 133$; 22.7%) in which a median OS was not reached and a 2-year OS was 75% (95% CI, 65%–82%). Patients with one or two adverse factors were in the intermediate-risk category ($n = 301$; 51.4%) in which a median OS was 27 months and a 2-year OS was 53% (95% CI, 46%–59%). Finally, those patients with three to six adverse factors were in the poor-risk category ($n = 152$; 25.9%) in which a median OS was 8.8 months and a 2-year OS was 7% (95% CI, 2%–16%).⁹⁸ This model was validated in an independent dataset.¹⁰⁰

Surgical Options for Patients with Relapsed or Stage IV Disease

Patients with stage IV disease also may benefit from surgery. For example, lymph nodes suspicious of metastatic disease on CT may be hyperplastic and not involved with the tumor; thus, the presence of minimal regional adenopathy does not preclude surgery.

Cytoreductive nephrectomy before systemic therapy is recommended in select patients with a potentially surgically resectable primary tumor mass. A retrospective analysis conducted in the cytokine era indicated that patients most likely to benefit from cytoreductive nephrectomy before systemic therapy were those with lung-only metastases, good prognostic features, and good performance status.¹⁰¹ Retrospective data from the IMDC suggested that cytoreductive nephrectomy continues to play a role in patients treated with VEGF-targeted agents.¹⁰² The efficacy of newer systemic therapies is challenging the standard in some patients with metastatic disease. Results from the CARMENA phase III trial of patients with metastatic RCC who were eligible for cytoreductive nephrectomy found that sunitinib alone was non-inferior to sunitinib after nephrectomy.¹⁰³ The median OS was 18.4 months in the sunitinib-alone group and 13.9 months in the sunitinib after nephrectomy group (HR, 0.89; 95% CI, 0.71–1.10), which did not exceed the fixed non-inferiority limit (1.20). However, many of the patients in this trial had poor-risk features, underscoring the importance of patient selection to obtain the greatest benefit from nephrectomy or targeted therapy.^{103,104} A post-hoc analysis of the CARMENA trial reported that for patients with only one IMDC risk factor, OS was longer following nephrectomy (31.4 months vs. 25.2 months).¹⁰⁵ At this point, there are no prospective data defining the role of cytoreductive nephrectomy in patients who subsequently receive checkpoint antibody therapy. Further study will better define the role of cytoreductive nephrectomy in the rapidly evolving treatment landscape for RCC.



NCCN Guidelines Version 2.2024

Kidney Cancer

Patients with metastatic disease who present with hematuria or other symptoms related to the primary tumor should be offered palliative nephrectomy if they are surgical candidates. In addition, the small subset of patients with potentially surgically resectable primary RCC and oligometastatic sites are candidates for nephrectomy and management of metastases by surgical metastasectomy; alternatively, ablative techniques are available for selected patients who are not candidates for metastasectomy. Candidates include patients who: 1) initially present with primary RCC and oligometastatic sites; or 2) develop oligometastases after a prolonged disease-free interval from nephrectomy. Oligometastatic sites that are amenable to this approach include the lung, bone, and brain. The primary tumor and the metastases may be resected during the same operation or at different times. Most patients who undergo targeted treatment of oligometastases experience recurrence, but long-term relapse-free survival has been reported in these patients.

In patients whose tumors are surgically unresectable, the panel recommends performing tissue sampling to confirm diagnosis of RCC to determine histology and guide subsequent management. Systemic therapy is generally recommended after recurrence, after cytoreductive nephrectomy in patients with multiple metastatic sites, or for patients with surgically unresectable tumors.

Patients who have undergone a nephrectomy and years later develop an oligometastatic recurrence also have the option of metastasectomy, SBRT,¹⁰⁶⁻¹⁰⁸ or ablative techniques, in addition to the first-line therapy options below.

Systemic Therapy Options for Patients with Relapsed or Stage IV Disease

Targeted therapy utilizing TKIs, and/or anti-VEGF antibodies, has been widely used in first- and second-line treatments. Agents targeting the mammalian target of rapamycin (mTOR) are also used in highly selected

settings. A number of targeted agents have been approved by the FDA for the treatment of advanced RCC in the first and/or subsequent lines of therapy. ICIs provided a revolution in treatment options. Checkpoint antibodies alter the interaction between immune cells and antigen-presenting cells, including tumor cells. These agents can augment an anti-tumor immune response and have shown promise in a number of tumor indications.

Tumor histology and risk stratification of patients is important in therapy selection. The NCCN Guidelines for Kidney Cancer stratify treatment recommendations by histology. Recommendations for first-line treatment of ccRCC are also stratified by risk group.

NCCN Categories of Preference

To further guide management of advanced RCC, the NCCN Kidney Cancer Panel has categorized all systemic kidney cancer therapy regimens as “Preferred,” “Other Recommended Regimens,” or “Useful in Certain Circumstances.” This categorization provides guidance on treatment selection by considering the efficacy, safety, evidence, and other factors that play a role in treatment selection. These factors include pre-existing comorbidities, nature of the disease, and in some cases consideration of access to agents.

Data Tables According to Line of Treatment and RCC Histology (Key Studies)

Due to the increasing number of NCCN-recommended systemic therapy options for metastatic RCC, the panel has organized efficacy data from key studies into tables according to RCC histology and line of treatment (when applicable) for category 1 and 2A, preferred, and other recommended regimens; see *Table 1*, *Table 2*, and *Table 3* in this Discussion.



NCCN Guidelines Version 2.2024

Kidney Cancer

Information about drug mechanism of action, FDA approval, summaries of study conclusions and safety data, and Categories of Evidence and Consensus and Categories of Preference for NCCN-recommended regimens remains below, and is stratified by RCC histology, line of treatment (when applicable), prior immuno-oncology (IO) therapy status (when applicable), and Category of Preference.

First-Line Systemic Therapy Options for Patients with Clear Cell RCC (ccRCC)

Preferred Regimens

Axitinib with Pembrolizumab (All Risk Groups)

Axitinib is a selective, second-generation TKI of vascular endothelial growth factor receptors (VEGFRs), while pembrolizumab is a monoclonal antibody that selectively binds to PD-1 (expressed on activated T cells) and blocks the interaction between PD-1 and its ligands programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2; both expressed on antigen-presenting cells). In April 2019, the FDA approved axitinib in combination with pembrolizumab for first-line treatment of patients with advanced RCC.^{109,110} Data from the randomized phase III KEYNOTE-426 trial, which included patients with favorable-, intermediate-, or poor-risk RCC, supported the combination therapy's approval for this indication (see *Table 1* for efficacy data). Patients received either axitinib/pembrolizumab or sunitinib; those receiving the combination regimen had a significantly higher overall response rate (ORR) and longer PFS than those receiving sunitinib. Median OS was not reached for either group, but the HR favored axitinib/pembrolizumab.¹¹¹ A subsequent exploratory analysis with a 31-month median follow-up period showed agreement with these data.¹¹² Based on these data, the panel recommends first-line axitinib/pembrolizumab as a category 1, preferred option for patients with ccRCC across all risk groups.

Cabozantinib with Nivolumab (All Risk Groups)

Cabozantinib is a multitargeted TKI of VEGFRs, MET, and AXL, while nivolumab is an anti-PD-1 antibody. In January 2021, the FDA approved cabozantinib in combination with nivolumab for first-line treatment of patients with advanced RCC.¹¹³ Data from the randomized phase III CheckMate 9ER trial, which included patients with favorable-, intermediate-, or poor-risk RCC, supported the combination therapy's approval for this indication (see *Table 1* for efficacy data). Patients received either cabozantinib/nivolumab or sunitinib; those receiving cabozantinib/nivolumab had significantly longer ORR and PFS than those receiving sunitinib. Median OS was not reached for either group, but the HR favored cabozantinib/nivolumab.^{112,114} In an updated analysis, the cabozantinib/nivolumab arm showed improved PFS, OS, and ORR in advanced RCC patients with sarcomatoid features (an aggressive histologic subtype associated with poor prognosis) when compared to sunitinib.¹¹⁵ Patients in combination also reported delayed time to deterioration of patient-reported outcome scores compared to sunitinib.¹¹⁶ Based on these data, the panel recommends first-line cabozantinib/nivolumab as a category 1, preferred option for patients with ccRCC across all risk groups.

Lenvatinib with Pembrolizumab (All Risk Groups)

Lenvatinib is a multitargeted TKI of VEGFR-1, -2, and -3; fibroblast growth factor receptor (FGFR)-1, -2, -3, and 4; platelet-derived growth factor receptor- α (PDGFR- α); c-KIT; and RET. Pembrolizumab's mechanism of action was described previously. In August 2021, the FDA approved lenvatinib in combination with pembrolizumab for first-line treatment of patients with advanced RCC.¹¹⁷ Data from the randomized phase III CLEAR trial, which included patients with favorable-, intermediate-, or poor-risk RCC, supported the combination therapy's approval for this indication (see *Table 1* for efficacy data). Patients received either lenvatinib/pembrolizumab, lenvatinib/everolimus, or sunitinib. Those



NCCN Guidelines Version 2.2024

Kidney Cancer

receiving lenvatinib/pembrolizumab had significantly longer PFS and a higher ORR than those receiving sunitinib. Median OS was not reached for either group, but the HR for lenvatinib/pembrolizumab versus sunitinib favored the combination regimen. In contrast, OS was not significantly different between the lenvatinib/everolimus and sunitinib groups.¹¹⁸ Based on these data, the panel recommends first-line lenvatinib/pembrolizumab as a category 1, preferred treatment option for patients with ccRCC across all risk groups.

Ipilimumab with Nivolumab (Poor-/Intermediate-Risk Groups)

Ipilimumab is a monoclonal antibody that selectively blocks the interaction between the negative regulator cytotoxic T-lymphocyte antigen 4 (CTLA-4; expressed early on activated T cells) and its ligands CD80/CD86 (expressed on antigen-presenting cells); nivolumab's mechanism of action was described previously. In April 2018, the FDA approved ipilimumab in combination with nivolumab for first-line treatment of patients with poor-/intermediate-risk advanced RCC.¹¹⁹ Data from the randomized phase III CheckMate 214 trial, which supported the FDA approval, compared combination ipilimumab/nivolumab followed by nivolumab monotherapy with sunitinib monotherapy in patients with advanced RCC.¹²⁰ The study's coprimary endpoints were ORR, OS, and PFS in intermediate- and poor-risk patients only; exploratory analyses of data in favorable-risk patients were reported separately (see *Table 1* and ccRCC: *First-Line, Other Recommended Regimens*). In intermediate-/poor-risk patients, combination ipilimumab/nivolumab led to a higher ORR and CR rate versus sunitinib monotherapy. Median PFS did not meet the prespecified threshold, and was not statistically significant between the two treatment arms. Treatment-related AEs occurred in 93% of patients in the ipilimumab/nivolumab group and 97% of patients in the sunitinib group; grade 3 or 4 events occurred in 46% and 63%, respectively. AEs led to treatment discontinuation in 22% and 12% of patients receiving ipilimumab/nivolumab and sunitinib, respectively. Treatment-related

deaths occurred in 8 patients receiving the combination therapy and 4 patients receiving sunitinib. Thirty-five percent of patients who developed immune-mediated AEs after ipilimumab/nivolumab treatment received high-dose steroids.¹²⁰ Based on these data, the panel recommends first-line ipilimumab/nivolumab as a category 1, preferred treatment option for poor- and intermediate-risk patients with ccRCC.

Cabozantinib (Poor-/Intermediate-Risk Groups)

In the open-label, randomized phase II CABOSUN trial, patients with intermediate- or poor-risk advanced RCC received either cabozantinib or sunitinib. See *Table 1* for efficacy data. Those treated with cabozantinib showed a significantly increased median PFS and higher ORR compared to those treated with sunitinib.¹²¹ Based on these results, the panel recommends first-line cabozantinib as a category 2A, preferred treatment option for poor- and intermediate-risk patients with ccRCC.

Other Recommended Regimens

Axitinib with Avelumab (All Risk Groups)

Avelumab is a monoclonal antibody that selectively binds to PD-L1; axitinib's mechanism of action was described previously. In May 2019, the FDA approved axitinib/avelumab for first-line treatment of patients with advanced RCC. Data from the randomized phase III JAVELIN Renal 101 trial, which included patients with favorable-, intermediate-, or poor-risk RCC, supported the combination therapy's approval for this indication (see *Table 1* for efficacy data).^{122,123} For both the overall population and PD-L1-positive patients, those receiving axitinib/avelumab had significantly longer PFS than those receiving sunitinib. This benefit was observed across all risk groups. For median OS, data were immature for all groups in both the primary¹²² and 13-month interim¹²³ analyses. Based on these results, the panel added first-line axitinib/avelumab as a category 2A, other recommended regimen for patients with ccRCC across all risk groups. The post-hoc analysis of 108 patients with sarcomatoid histology in the phase



NCCN Guidelines Version 2.2024

Kidney Cancer

III JAVELIN Renal 101 trial showed that patients in the avelumab/axitinib treatment arm had improved PFS (stratified HR, 0.57; 95% CI, 0.325–1.003) and a higher objective response rate (46.8% vs. 21.3%; complete response [CR] in 4.3% vs. 0%) versus those in the sunitinib arm.¹²⁴

Cabozantinib (Favorable-Risk Group)

Extrapolating on the CABOSUN data for poor-/intermediate-risk patients (see above), the panel added first-line cabozantinib as a category 2B, other recommended regimen for favorable-risk patients with ccRCC.

Ipilimumab with Nivolumab (Favorable-Risk Group)

The CheckMate 214 trial included favorable-risk patients treated with ipilimumab/nivolumab or sunitinib (see *Table 1* for efficacy data). The 18-month OS in poor-/intermediate-risk patients favored ipilimumab/nivolumab over sunitinib, but an exploratory analysis of OS data from favorable-risk patients favored sunitinib over the combination regimen. ORR and median PFS were also lower in favorable-risk patients receiving ipilimumab/nivolumab than those receiving sunitinib. However, CR rates were higher in favorable-risk patients than in poor-/intermediate-risk patients, regardless of treatment regimen.^{120,125}

Based on these data, the panel recommends first-line combination ipilimumab/nivolumab as a category 2A, other recommended regimen for favorable-risk patients with ccRCC. As mentioned above, the FDA approval for ipilimumab/nivolumab is narrower, only including patients with intermediate- or poor-risk ccRCC.

Pazopanib (All Risk Groups)

Pazopanib is an oral multitargeted TKI/angiogenesis inhibitor of VEGFRs, PDGFR- α and - β , and stem cell factor receptor (c-KIT). The drug's safety and efficacy were evaluated in an open-label phase III study. Patients with advanced ccRCC who received 0–1 prior treatment received either pazopanib or placebo (see *Table 1* for efficacy data). PFS was

significantly longer and ORR was significantly higher with pazopanib versus placebo in the treatment-naïve sub-population,¹²⁶ but there was no difference in OS between the two groups.¹²⁷ Notable grade 3 toxicity was hepatotoxicity, indicated by elevated levels of alanine (30%) and aspartate (21%) transaminase.¹²⁶ Therefore, it is critical to monitor liver function before and during treatment with the drug.

Additionally, the COMPARZ non-inferiority study of sunitinib versus pazopanib showed that these two drugs have similar safety and efficacy (see *Table 1* for efficacy data).^{128,129} Based on these data, the panel has listed first-line pazopanib as a category 2A, other recommended regimen for patients with ccRCC across all risk groups.

Sunitinib (All Risk Groups)

Sunitinib is a multikinase inhibitor targeting several receptor tyrosine kinases, including PDGFR- α and - β ; VEGFR-1, -2, and -3; c-KIT; FMS-like tyrosine kinase 3 (FLT3); colony-stimulating factor-1 receptor (CSF-1R); and neurotrophic factor receptor (RET).^{130–133} The efficacy of first-line sunitinib was studied in a randomized phase III trial, in which patients with metastatic RCC received either sunitinib or IFN- α .¹³⁰ See *Table 1* for efficacy data. Median PFS was longer in those receiving sunitinib across all risk groups. Updated results demonstrated a strong trend towards OS advantage of sunitinib over IFN- α in the first-line setting.¹³⁴ Based on these data, the panel includes first-line sunitinib as a category 2A, other recommended regimen for patients with ccRCC across all risk groups.

Useful in Certain Circumstances Treatments

Active Surveillance for Select, Asymptomatic Patients with ccRCC

A subset of patients with advanced ccRCC show indolent progression of disease and could benefit from initial active surveillance because of the toxicity of systemic therapies. A phase II trial of patients with treatment-naïve, asymptomatic, metastatic RCC followed patients on active



NCCN Guidelines Version 2.2024

Kidney Cancer

surveillance through radiographic assessment at defined intervals until a decision was made to initiate systemic therapy.¹³⁵ Of the 48 patients included in the analysis, the median time of surveillance from registration to initiation of systemic therapy was 14.9 months. This study demonstrated that a subset of patients with advanced ccRCC can safely undergo active surveillance before starting systemic therapy. Therefore, the panel included active surveillance as a category 2A, useful in certain circumstances option for select, asymptomatic patients with favorable-risk ccRCC.

Axitinib (All Risk Groups)

As a second-line therapy for patients with ccRCC, axitinib treatment led to higher ORR and longer median PFS compared with sorafenib.¹³⁶ In a randomized phase III trial, treatment-naïve patients received either axitinib or sorafenib; median PFS was not significantly longer in patients receiving axitinib versus sorafenib but had an acceptable toxicity profile.¹³⁷ Based on these data, the panel has included first-line axitinib as a category 2B, useful in certain circumstances option for patients with ccRCC across all risk groups.

High-Dose IL-2 (All Risk Groups)

IL-2-based immunotherapy achieved long-lasting complete or partial remissions in a small subset of patients, but high-dose IL-2 is associated with substantial toxicity, and attempts to characterize tumor or patient factors for best response to this therapy have been unsuccessful.¹³⁸⁻¹⁴⁰ For highly selected patients with ccRCC, first-line high-dose IL-2 has been designated as useful in certain circumstances (category 2B designation for favorable-risk patients and category 3 for poor-/intermediate-risk patients).

Temsirolimus (Poor-/Intermediate-Risk Patients)

Temsirolimus is an inhibitor of the mTOR protein. The randomized, open-label phase III ARCC study enrolled previously untreated patients with

advanced RCC who had three or more unfavorable prognostic factors.¹⁴¹ Patients received IFN- α alone, temsirolimus alone, or the combination of temsirolimus and IFN- α . Those who received temsirolimus alone showed improvement in OS and median PFS over those receiving IFN- α alone or combination therapy. Based on these data, the panel has included first-line temsirolimus as a category 3, useful in certain circumstances option for poor- and intermediate-risk patients with ccRCC.

Subsequent Systemic Therapy Options for Patients with Clear Cell RCC (ccRCC)

The NCCN Kidney Cancer Panel recently stratified the subsequent therapies for ccRCC based on whether the patients have received any prior IO therapy. The recommended options are now further categorized into “IO therapy naïve” and “prior IO therapy.” In addition, the panel removed a category 1 designation from the respective regimens in the subsequent therapy table (ie, axitinib, cabozantinib, nivolumab, tivozanib). This is due to the panel’s observation that randomized registration trials for these monotherapies began prior to the approval of IO combination therapy, and very few patients enrolled on these trials received upfront IO combination therapy. Therefore, the data no longer support the category 1 level evidence for subsequent monotherapy after frontline TKIs in the era of IO combination therapy, despite the lack of phase 3 trial data for combinations in this setting.

Cabozantinib

In the randomized phase III METEOR trial, patients with disease progression after previous TKI therapy received cabozantinib or everolimus. See Table 2 for efficacy data. Median PFS was significantly longer and ORR significantly higher in patients receiving cabozantinib versus everolimus.¹⁴² The final analysis of the METEOR trial showed a



NCCN Guidelines Version 2.2024

Kidney Cancer

statistically significant increase in OS in the cabozantinib arm versus the everolimus arm.^{143,144}

Additionally, a network meta-analysis comparing the relative effectiveness of subsequent treatment options for RCC found the probability of longer PFS during the analyzed 3 years to be higher with cabozantinib compared to everolimus, nivolumab, axitinib, sorafenib, and best supportive care.¹⁴⁵ Based on these data, the panel has included cabozantinib as a subsequent therapy option under “other recommended regimens” for patients with ccRCC regardless of their prior IO therapy status.

Lenvatinib with Everolimus

In May 2016, the FDA approved lenvatinib, a multitargeted kinase inhibitor, in combination with everolimus, an mTOR inhibitor, for treating advanced RCC following one prior anti-angiogenic therapy.^{146,147} In a randomized phase II trial, patients with metastatic or unresectable, locally advanced ccRCC who had received prior antiangiogenic therapy received either combination lenvatinib/everolimus, single-agent lenvatinib, or single-agent everolimus. See *Table 2* for efficacy data. PFS and median OS were significantly longer in patients receiving lenvatinib/everolimus versus everolimus monotherapy.^{148,149} Based on the phase II trial data, the panel considers lenvatinib/everolimus a subsequent therapy option under “other recommended regimens” for patients with ccRCC regardless of their prior IO therapy status.

Nivolumab

In the randomized phase III CheckMate 025 trial, patients with advanced ccRCC who were previously treated with one or more lines of therapy (excluding mTOR inhibitors) received either nivolumab or everolimus. See *Table 2* for efficacy data. Patients receiving nivolumab had significantly longer OS and significantly higher ORR than those receiving everolimus.¹⁵⁰ An independent analysis was carried out to determine the

efficacy of nivolumab-based baseline factors such as number and location of metastases, risk group, number of prior therapies, and specific prior therapies (ie, sunitinib, pazopanib, IL-2); a consistent OS benefit and ORR were observed across all baseline factors.¹⁵¹ Based on these data, the panel has included nivolumab as a category 2A, subsequent therapy option for patients with ccRCC who have not received any prior IO therapy.

Axitinib

The randomized phase III AXIS study compared second-line axitinib versus sorafenib. See *Table 2* for efficacy data. Median PFS was significantly longer and ORR significantly higher in patients receiving axitinib versus sorafenib.¹³⁶ Updated AXIS results showed that while OS did not significantly differ between the two groups, patients receiving axitinib had a continued improvement in PFS.¹⁵² Based on these data, the panel included axitinib as a category 2A other recommended subsequent therapy option for patients with prior IO therapy and useful in certain circumstances for patients naïve for any prior IO therapy.

Axitinib with Pembrolizumab

Upon axitinib/pembrolizumab’s FDA approval in a first-line setting,^{109,110} the panel discussed whether the combination therapy might be used in clinical practice as an off-label subsequent treatment option in patients with relapsed or stage IV ccRCC. While they conceded that there were no published data to support the use of axitinib/pembrolizumab in a second-line setting, they thought that clinicians were likely to consider the combination as a treatment option in patients with advanced ccRCC whose disease progressed after first-line sunitinib therapy. The panel added axitinib/pembrolizumab as a category 2A, other recommended option for patients who are IO therapy naïve and useful in certain circumstances for patients with prior IO therapy.



NCCN Guidelines Version 2.2024

Kidney Cancer

Cabozantinib with Nivolumab

Apolo et al 2020¹⁵³ published data from an ongoing phase I dose escalation trial (ie, NCT02496208) in which patients with metastatic urothelial carcinoma or other genitourinary tumors (including three patients with ccRCC) received combination cabozantinib/nivolumab with or without ipilimumab; data from patients with ccRCC were not reported separately. In 2021, a conference abstract¹⁵⁴ reported a pooled analysis of the phase I dose-finding cohort and seven subsequent expansion cohorts, which included 16 patients with metastatic RCC. See *Table 2* for efficacy data. In these patients, median OS was 38.6 months (95% CI, 19.4–not estimable [NE]). The panel added cabozantinib/nivolumab as a category 2A, other recommended option for patients who are IO therapy naïve and useful in certain circumstances for patients with prior IO therapy.

Ipilimumab with Nivolumab

The phase I CheckMate 016 trial included treatment-naïve patients and those who had received one to four or more prior treatment regimens. See *Table 2* for efficacy data. Only the ORR results were stratified by treatment status: ORR in the N3I1 and N1I3 was approximately 46% and 39%, respectively. OS and PFS data were not stratified by treatment line, but were similar.¹⁵⁵ Based on these data, the panel considers ipilimumab/nivolumab as a category 2A, other recommended option for patients who are IO therapy naïve and useful in certain circumstances option for patients with prior IO therapy.

Lenvatinib with Pembrolizumab

The ongoing phase II KEYNOTE-146 trial included three groups of patients: treatment-naïve; those who had previously received at least one line of treatment that did not include anti-PD-1 or anti-PD-L1 ICIs; and those who had previously received at least one anti-PD-1 or anti-PD-L1 ICI. See *Table 2* for efficacy data. Treatment-naïve patients had the highest ORR and the longest PFS; ORR and PFS were comparable in the

ICI-naïve and ICI treatment-experienced groups. Median OS was only met in the ICI-naïve group.¹⁵⁶ Based on these data, the panel considers lenvatinib/pembrolizumab a category 2A, other recommended option for patients who are IO therapy naïve and useful in certain circumstances option for patients with prior IO therapy.

Pazopanib

A phase III trial comparing pazopanib with placebo, detailed earlier under the *ccRCC: First-Line, Other Recommended Regimens*, also included patients who had received prior cytokine therapy. See *Table 2* for efficacy data. PFS was significantly longer with pazopanib versus placebo in the treatment-experienced sub-population,¹²⁶ but OS was similar between the two groups.¹²⁷ Additionally, a prospective phase II trial evaluated second-line pazopanib in patients with advanced metastatic RCC previously treated with a targeted agent (ie, bevacizumab, sunitinib). Twenty-seven percent of patients had an objective response to pazopanib; 49% had stable disease (SD). Median PFS was 7.5 months, regardless of prior treatment regimen. Estimated OS rate at 24 months was 43%.¹⁵⁷ Based on these data, the panel considers pazopanib a category 2A, useful in certain circumstances subsequent therapy option for patients with ccRCC regardless of their prior IO therapy status.

Sunitinib

Sunitinib also has demonstrated substantial anti-tumor activity as a second-line therapy in patients with metastatic RCC who progressed on cytokine therapy.^{131,158} Studies investigating the sequential use of sunitinib and sorafenib are mostly retrospective. There are limited prospective data that suggest a lack of total cross-resistance between TKIs, either sorafenib followed by sunitinib failures or vice versa—an observation that is consistent with their differences in target specificities and slightly different toxicity spectra that sometimes permit tolerance of one agent over another.^{159–163} Sunitinib is considered a category 2A, useful in certain



NCCN Guidelines Version 2.2024

Kidney Cancer

circumstances subsequent therapy option for patients with ccRCC regardless of their prior IO therapy status.

Tivozanib

In March 2021, the FDA approved tivozanib, a multitargeted TKI, for patients with relapsed or refractory advanced RCC who previously received two or more systemic therapies.¹⁶⁴ Data from the randomized phase III TIVO-3 trial, which enrolled treatment-experienced patients with relapsed or refractory advanced ccRCC, supported the drug's approval. See *Table 2* for efficacy data. Patients receiving tivozanib had significantly longer PFS than those receiving sorafenib; OS was similar between the two groups.¹⁶⁵ In a recently updated analysis, tivozanib also increased quality-adjusted time without symptoms of disease and toxicity (Q-TWiST) as compared to sorafenib (15.04 months vs. 12.78 months, respectively).¹⁶⁶ Based on these data, the panel considers tivozanib as a category 2A, other recommended subsequent therapy option for patients who have received prior IO therapy and a useful in certain circumstances option for those who are IO therapy naive.

Axitinib with Avelumab

Extrapolating on the first-line JAVELIN Renal 101 data for poor-/intermediate-risk patients (see *ccRCC: First-Line, Other Recommended Regimens*), the panel added axitinib/avelumab as a category 3, useful in certain circumstances subsequent therapy option for patients with ccRCC regardless of their prior IO therapy status.

Everolimus

Everolimus (RAD001) is an orally administered mTOR inhibitor. In the randomized phase III RECORD-1 trial, everolimus was compared with placebo for the treatment of metastatic RCC in patients whose disease had progressed on treatment with sunitinib or sorafenib. The median PFS was significantly longer for everolimus versus placebo, but OS was similar

between the two groups.^{167,168} Everolimus is listed as a category 2A, useful in certain circumstances subsequent therapy option for patients with ccRCC regardless of their prior IO therapy status.

Bevacizumab

Phase II trials have shown benefit of bevacizumab monotherapy after prior treatment with a cytokine.¹⁶⁹ Bevacizumab is a category 2B, useful in certain circumstances subsequent therapy option for patients with ccRCC regardless of their prior IO therapy status.

High-Dose IL-2 (for selected patients)

High-dose IL-2 is listed as a category 2B, useful in certain circumstances subsequent therapy option for selected patients with excellent performance status and normal organ function regardless of their prior IO therapy status.

Sorafenib

Sorafenib tosylate is a small molecule that inhibits multiple isoforms of the intracellular serine/threonine kinase, RAF, and other receptor tyrosine kinases, including VEGFR-1, -2, and -3; PDGFR-β; FLT3; c-KIT; and RET.¹⁷⁰⁻¹⁷⁴ Efficacy of sorafenib was studied in the randomized phase III TARGET trial, which enrolled patients with ccRCC who progressed on a prior therapy (mostly cytokines). Sorafenib-treated patients had significantly longer OS and PFS than those receiving placebo.^{175,176} The panel consensus did not support the inclusion of sorafenib as a subsequent therapy option for ccRCC.

Tensirolimus

The randomized phase III INTORSECT trial compared the efficacy of temsirolimus to sorafenib following first-line sunitinib as a treatment for patients with ccRCC or nccRCC. While a significant OS advantage was observed for sorafenib, PFS was similar between the two groups.¹⁷⁷ The panel considers temsirolimus a category 2B, useful in certain



NCCN Guidelines Version 2.2024

Kidney Cancer

circumstances subsequent therapy option for patients with ccRCC regardless of their prior IO therapy status.

Belzutifan

Belzutifan inhibits the transcription factor hypoxia-inducible factors 2 α (HIF-2 α) and blocks the heterodimerization of HIF-2 α with HIF-2 β , thereby inducing tumor regression. Follow-up from an expansion cohort of patients, with ccRCC in a phase I/II trial of belzutifan, who had received 1 or more prior therapies showed a disease control rate of 80% among 55 patients. Median PFS was 14.5 months with 51% reporting PFS of 12 months. Most common AEs reported were anemia, fatigue, and dyspnea, among others.¹⁷⁸ Based on these results, belzutifan was considered well tolerated with a favorable safety profile as a single agent. A phase III trial of belzutifan compared to everolimus in patients with aRCC that has progressed after first-line therapies is underway (NCT04195750). The panel considers belzutifan a category 2B, useful in certain circumstances subsequent therapy option for patients with ccRCC regardless of their prior IO therapy status.

Systemic Therapy for Patients with Non-Clear Cell RCC (nccRCC)

Clinical trials of targeted agents have predominantly focused on patients with clear cell RCC due to the high prevalence of ccRCC.¹⁷⁹ Data from systematic reviews, meta-analyses, and phase II studies with targeted agents also show some activity in patients with nccRCC. Compared with responses in ccRCC, however, the response rates with these agents are significantly lower for nccRCC. Therefore, according to the panel, enrollment in clinical trials is the preferred strategy for nccRCC.

nccRCC: Preferred Regimens

Cabozantinib

The randomized phase II SWOG 1500 trial compared the MET-targeted TKIs cabozantinib, crizotinib, and savolitinib with standard-of-care sunitinib

in patients with advanced papillary RCC who had previously received up to 1 previous systemic therapy, excluding VEGF- and MET-targeted TKIs. Assignment to the crizotinib and savolitinib arms was halted due to results of a prespecified futility analysis.¹⁸⁰ See *Table 3* for efficacy data. Patients receiving cabozantinib had significantly longer PFS and a higher ORR than those receiving sunitinib. Based on these data, the panel included cabozantinib as a category 2A, preferred option for patients with nccRCC.

Sunitinib

Two recent randomized phase II studies compared first-line sunitinib with first-line everolimus in patients with nccRCC. See *Table 3* for efficacy data. While data from the ASPEN trial¹⁸¹ suggested that patients receiving sunitinib had significantly longer PFS than those receiving everolimus, data from the ESPN trial¹⁸² suggested that both OS and PFS were similar between the two groups.

Additionally, a meta-analysis of randomized clinical trials for patients with nccRCC found that TKI treatment reduced the risk of progression compared with mTOR inhibitors.¹⁸³ The study found that sunitinib significantly reduced the risk of progression compared to everolimus in the first-line setting. However, no significant differences between TKIs and mTOR inhibitor treatment were found for OS and ORR. Based on these data, sunitinib is listed as a category 2A, preferred option for patients with nccRCC.

nccRCC: Other Recommended Regimens

Lenvatinib with Everolimus

Extrapolating on data from the phase III lenvatinib/everolimus trial in patients with ccRCC¹⁴⁸ (see *ccRCC: Subsequent, Preferred Regimens*), the panel added the combination therapy as a category 2A, other recommended regimen for patients with nccRCC.



NCCN Guidelines Version 2.2024

Kidney Cancer

They also reviewed data¹⁸⁴ from an ongoing single-arm phase II trial (ie, NCT02915783) enrolling patients with unresectable advanced or metastatic nccRCC who had not previously received prior systemic therapy; all patients in the trial received combination lenvatinib/everolimus. See *Table 3* for efficacy data. Authors reported that ORR was 26% (95% CI, 12–45). Eight patients in the trial achieved a PR (papillary, n = 3; chromophobe, n = 4; unclassified, n = 1); no patients had a CR. The median duration of response was NE. Eighteen patients (58.1%) had SD, and the clinical benefit rate (CR + partial response [PR] + durable SD [duration ≥23 weeks]) was 61% (95% CI, 42–78). The median PFS was 9.2 months (95% CI, 5.5–NE) and OS was 15.6 months (95% CI, 9.2–NE). While the panel conceded that the number of enrolled patients was small, they generally felt that lenvatinib/everolimus treatment led to improved patient outcomes across all nccRCC subtypes.

Nivolumab

A retrospective analysis evaluated the response to at least one dose of nivolumab in patients with metastatic nccRCC.¹⁸⁵ See *Table 3* for efficacy data. This study evaluated 35 patients for response and found that 20% had a PR and 29% had SD, with a median follow-up of 8.5 months and median PFS of 3.5 months. A separate retrospective analysis found modest responses with PD-1/PD-L1 inhibitors in 43 patients also with metastatic nccRCC.¹⁸⁶ An objective response was achieved in eight patients (19%), including four patients (13%) who received PD-1/PD-L1 monotherapy. Based on these data, the panel considers nivolumab a category 2A, other recommended regimen for patients with nccRCC.

Nivolumab with Cabozantinib

Two separate patient cohorts defined by nccRCC histology in a phase II open-label trial received nivolumab/cabozantinib combination.¹⁸⁷ ORR for patients with papillary, unclassified, or translocation RCC was 48% with a median follow-up time of 13.1 months. Median PFS was 12.5 months

(95% CI, 6.3–16.4) and median OS was 28 months (95% CI, 16.3–NE). Study of patients with chromophobe RCC closed early due to the lack of efficacy. Based on these results, the panel added nivolumab/cabozantinib under other recommended options as first or subsequent-line treatment of relapse or stage IV nccRCC.

Pembrolizumab

Cohort B of the phase II KEYNOTE-427 study assessed the efficacy and safety of pembrolizumab monotherapy in 165 patients with systemic therapy-naïve, newly diagnosed or recurrent stage IV nccRCC.¹⁸⁸ See *Table 3* for efficacy data. The majority (about 72%) of patients had confirmed papillary RCC, about 13% had chromophobe RCC, and about 16% had unclassified RCC histology. ORR across all subtypes was approximately 27% (ORR by histology was 29% for papillary, 10% for chromophobe, and 31% for unclassified). Overall PFS and OS were 4.2 months and 28.9 months, respectively. Based on these data, the panel added pembrolizumab as a category 2A, other recommended regimen for patients with nccRCC.

nccRCC: Useful in Certain Circumstances Regimens

Axitinib

A phase II trial of axitinib in 40 patients with recurrent or metastatic nccRCC that failed treatment with temsirolimus found a median PFS of 7.4 months and ORR of 37.5%.¹⁸⁹ The panel considers axitinib a category 2A, useful in certain circumstances option for patients with nccRCC.

Bevacizumab

A small phase II trial studied bevacizumab monotherapy in patients with papillary RCC. The PFS reported for each of these patients was 25, 15, 11, 10, and 6 months.¹⁹⁰ The panel has included bevacizumab as a category 2A, useful in certain circumstances option for patients with nccRCC.



NCCN Guidelines Version 2.2024

Kidney Cancer

Bevacizumab with Erlotinib for Advanced Papillary RCC, Including Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)-Associated RCC

HLRCC is a hereditary condition in which affected patients are at risk for development of skin and uterine leiomyomas, as well as an aggressive form of papillary kidney cancer.¹⁹¹ Bevacizumab in combination with either erlotinib or everolimus is currently being investigated for treatment of advanced papillary RCC, including HLRCC.

An abstract detailed the results of a phase II trial of patients with advanced papillary RCC (HLRCC-associated RCC; n = 42 or sporadic papillary RCC; n = 41) treated with bevacizumab plus erlotinib.¹⁹² All enrolled patients received two or fewer VEGFR TKIs; 27 (33%) had at least one prior treatment. The majority of patients had intermediate-risk disease. The ORR was 64% for those with HLRCC compared to 37% with sporadic papillary RCC. Median PFS was 21.1 months in the HLRCC group compared to 8.7 months in the sporadic papillary RCC group.¹⁹² Based on these data, the panel recommends bevacizumab plus erlotinib as a category 2A, useful in certain circumstances option for select patients with nccRCC and papillary histology, including HLRCC.

Bevacizumab with Everolimus

A phase II trial of 34 treatment-naïve patients with metastatic nccRCC studied the efficacy and safety of treatment with bevacizumab plus everolimus.¹⁹³ Median PFS, OS, and ORR were 11.0 months, 18.5 months, and 29%, respectively. Patients with tumors that contained appreciable papillary or chromophobe elements showed significantly higher PFS and ORR than other histologies.¹⁹⁴ Based on these data, the panel recommends bevacizumab plus everolimus as a category 2A, useful in certain circumstances option for patients with nccRCC.

Erlotinib

The efficacy of erlotinib, an oral epidermal growth factor receptor (EGFR) TKI, was studied in 52 patients with advanced papillary RCC.¹⁹⁵ ORR was 11% (5 of 45 patients; 95% CI, 3%–24%), and the disease control rate (defined as SD for 6 weeks, or confirmed PR or CR using RECIST) was 64%. Median OS was 27 months.¹⁹⁵ Based on these data, the panel has included erlotinib as a category 2A, useful in certain circumstances option for patients with nccRCC.

Everolimus

The efficacy and safety of everolimus in patients with metastatic nccRCC were evaluated in a subgroup of 75 patients enrolled in the REACT trial. ORR and rate of SD were similar between patients with ccRCC and nccRCC.¹⁹⁶ In a phase II study of treatment-experienced patients with nccRCC,¹⁹⁷ OS was 14 months and PFS was 5.2 months. According to data from the phase II RAPTOR trial,¹⁹⁸ OS and PFS ranged from 24 to 28 months and PFS ranged from 5 to 8 months; patients with type 1 nccRCC had better responses than those with type 2 histology. Based on these data, the panel included everolimus as a category 2A, useful in certain circumstances option for patients with nccRCC.

Nivolumab with Ipilimumab

A cohort of 52 patients with advanced nccRCC of the phase 3/4 Checkmate 920 trial received four doses of nivolumab/ipilimumab combination followed by nivolumab for less than or equal to 2 years or until disease progression. With 24.1 months of minimum study follow-up, the ORR was 19.6% with a median PFS of 3.7 months and median OS of 21.2 months (95% CI, 16.6–NE).¹⁹⁹ Based on this retrospective clinical evidence, the panel added nivolumab/ipilimumab as category 2B option for advanced nccRCC. The ongoing large phase 2 SUNNIFORECAST trial of nivolumab/ipilimumab for previously untreated advanced nccRCC will provide additional data on this therapy.



NCCN Guidelines Version 2.2024

Kidney Cancer

Pazopanib

In a Korean phase II trial of pazopanib in 28 patients with locally advanced or metastatic nccRCC, eight patients achieved a confirmed PR with an ORR of 28%.²⁰⁰ A retrospective analysis of an Italian multicenter cohort of nccRCC patients found treatment with pazopanib to be effective and safe.¹⁹⁴ Based on these data, the panel considers pazopanib a category 2A, useful in certain circumstances option for patients with nccRCC. There is an ongoing clinical trial evaluating the efficacy of second-line pazopanib in patients with nccRCC.²⁰¹

Temsirolimus

A retrospective subset analysis of the global phase III ARCC trial demonstrated benefit of temsirolimus not only in ccRCC but also in nccRCC.^{141,202} In patients with nccRCC (predominantly papillary RCC), the median OS was 11.6 months with temsirolimus and 4.3 months with IFN- α . Randomized clinical trials in rarer subgroups of patients are often challenging. Consistent with the results of the ARCC trial, a case report of a patient with a diagnosis of metastatic chromophobe RCC that was refractory to treatment with sunitinib achieved durable clinical response lasting 20 months upon treatment with temsirolimus.²⁰³ Temsirolimus is a useful in certain circumstances option for nccRCC; it has a category 1 designation for poor-risk patients and a category 2A designation for favorable-/intermediate-risk patients.

Additional Treatment Options for Rare Types of nccRCC

Among the nccRCC histologies, renal medullary carcinoma (RMC) is extremely rare, comprising approximately 2% of all primary renal tumors in young people.^{204,205} Metastatic disease is seen at presentation in 67% to 95% of patients.²⁰⁴⁻²⁰⁶ Chemotherapy remains the focus of treatment for this subtype, although the prognosis remains dismal.

Collecting-duct carcinoma is also a very rare type of nccRCC, often presenting at an advanced stage of disease. Up to 40% of patients have metastatic spread at initial presentation, and most patients die within 1 to 3 years from the time of primary diagnosis.²⁰⁷⁻²¹⁰ Collecting duct carcinoma shares biologic features with urothelial carcinoma. In a multicenter prospective study, 23 patients with no prior therapy were treated with a combination of gemcitabine and either cisplatin or carboplatin.²¹¹ The results showed a response rate of 26% and an OS of 10.5 months.²¹¹

The panel notes that in patients with other nccRCC subtypes such as collecting duct or medullary subtypes, PRs to cytotoxic chemotherapy have been observed (gemcitabine in combination with carboplatin or cisplatin; or paclitaxel with carboplatin) as well as for other platinum-based chemotherapies currently used for urothelial carcinomas. Gemcitabine in combination with doxorubicin can also produce responses in patients with RMC.^{212-206,213} Oral targeted therapies generally do not produce responses in patients with RMC. Erlotinib in combination with bevacizumab can produce responses even in heavily pretreated patients with RMC. Outside of clinical trials, platinum-based chemotherapy regimens should be the preferred first-line therapy for RMC.

Follow-up Recommendations for Relapsed or Stage IV Disease and Surgically Unresectable Disease

The panel recommends a history and physical examination of patients every 6 to 16 weeks for patients receiving systemic therapy, or more frequently as clinically indicated. Other laboratory evaluations may be carried out as per the requirements for the therapeutic agent being used.

Imaging tests such as CT or MRI should be performed prior to initiating systemic treatment/observation; subsequent imaging may be performed every 6 to 16 weeks as per the physician's discretion, patient's clinical status, and therapeutic schedule. Imaging interval frequency should be altered according to rate of disease change and sites of active disease.



NCCN Guidelines Version 2.2024

Kidney Cancer

MRI (preferred) or CT of head at baseline can be considered, as clinically indicated. Annual surveillance scans can be performed at physician's discretion. The panel recommends additional imaging such as MRI of spine and bone scan as clinically indicated.

Supportive Care

Supportive care remains a mainstay of therapy for all patients with metastatic RCC ([See NCCN Guidelines for Palliative Care](#)). This includes surgery for patients with oligometastatic disease in the brain whose disease is well-controlled extracranially. Stereotactic radiotherapy, if available, is an alternative to surgery for limited-volume brain metastasis, and whole brain irradiation is recommended for those patients with multiple brain metastases.²¹⁴

Surgery also may be appropriate for selected patients with malignant spinal cord compression, or impending or actual fractures in weight-bearing bones, if the rest of the disease burden is limited or patients remain symptomatic. Also, radiation therapy along with bisphosphonates is considered for palliation, particularly for painful bone metastases. The frequency of clinic visits or radiographic and laboratory assessments depends on the individual needs of the patient.

Bone metastasis occurs in 30% to 40% of patients with advanced RCC.²¹⁵⁻²¹⁷ Bone lesions in patients with RCC are typically osteolytic and cause considerable morbidity, leading to skeletal-related events (SREs), including bone pain with need for surgery or radiotherapy, hypercalcemia, pathologic fractures, and spinal cord compression. Two studies of patients with bone metastases showed an improvement in bone pain using different radiotherapy modalities.^{218,219}

The role of bone-modifying agents such as bisphosphonates (eg, zoledronic acid) has been established in patients with various malignancies.^{220,221} The newer bone-modifying agent approved for use in

patients with RCC that has metastasized to the bone is the RANK-L inhibitor, denosumab. A phase III randomized trial directly compared the development of SREs on either denosumab or zoledronic acid in patients with multiple myeloma or bone metastases with a solid tumor (excluding breast or prostate cancer). The study enrolled 1776 patients with bone metastases from a wide range of cancer types, including patients with RCC (6%) not previously treated with a bisphosphonate.²²² Denosumab was reported to be non-inferior to zoledronic acid in delaying time to first on-study SRE (HR, 0.84; 95% CI, 0.71–0.98; $P = .0007$).²²²

The panel recommends a bisphosphonate or a RANK ligand inhibitor for selected patients with bony metastases and creatinine clearance greater than or equal to 30 mL/min. Daily supplemental calcium and vitamin D are strongly recommended. Treatment for the palliation of symptoms, especially in patients with marginal performance status and evidence of metastatic disease, includes optimal pain management ([See NCCN Guidelines for Adult Cancer Pain](#)).

Hereditary RCC Syndromes

While hereditary RCC is relatively rare (around 3% of all RCC cases),²²³ the Panel felt that it was important to provide recommendations for patients with a suspected or confirmed hereditary RCC syndrome. Accordingly, the Guidelines now describe seven of the most common hereditary RCC syndromes that may predispose patients to RCC: *BAP1* tumor predisposition syndrome (*BAP1*-TPDS), Birt-Hogg-Dubé syndrome (BHDS), HLRCC, hereditary papillary renal carcinoma (HPRC), hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome, tuberous sclerosis complex (TSC), and VHL disease. The Guidelines describe kidney-specific clinical features and manifestations of each of these syndromes and known associated genes/inheritance patterns. They also provide genetic testing, surveillance, and treatment recommendations for individuals who are suspected or confirmed to have a hereditary RCC



NCCN Guidelines Version 2.2024

Kidney Cancer

syndrome. While published data informed the majority of these recommendations, the panel also relied on the real-world experience and expertise of the hereditary subcommittee members to develop recommendations in instances of limited data.

The subcommittee notes that there are some syndromes associated with RCC that overlap with other cancers (eg, Cowden syndrome, Lynch syndrome). For Cowden and Lynch syndromes, the panel refers readers to the information provided in the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#). Future versions of the Guidelines may be expanded to include other hereditary syndromes such as microphthalmia-associated transcription factor (MITF)-associated cancer syndrome, which predisposes patients to melanoma and/or RCC.¹¹

The subcommittee also notes that patients with hereditary RCC syndromes often experience non-renal manifestations, but felt that input from clinicians from other specialties (eg, dermatology, endocrinology, neurology, ophthalmology, urology) would be necessary to provide consensus-based recommendations for all potential manifestations. Accordingly, the scope is currently limited to kidney-specific clinical features and manifestations, but the subcommittee identified specialists who may be helpful in managing non-renal manifestations in patients with a hereditary RCC syndrome. Recommendations for genetic testing, surveillance, and treatment vary according to the individual's personal and/or family history of a hereditary RCC syndrome or clinical diagnosis of RCC. Below is a summary of recommendations by patient population.

Genetic Testing and Surveillance Recommendations for Individuals with a Personal or Family History of an RCC Syndrome

The panel recommends that individuals with a personal or family history of an RCC syndrome should undergo genetic evaluation. For criteria to be met for further genetic risk evaluation for hereditary RCC syndromes, see *HERED-RCC-1* in the NCCN Guidelines for Kidney Cancer. If patients

harbor a pathogenic or likely pathogenic genetic mutation associated with an RCC syndrome, they should undergo screening for the development of RCC.

For kidney-specific screening in patients who are confirmed to have a hereditary RCC syndrome but who do not yet have a radiographic or pathologic diagnosis of RCC, the panel recommends use of MRI (preferred). CT may also be used for surgical planning purposes, but the panel warns that use of abdominal CT should be limited due to the potential of increased lifetime radiation exposure. The panel also includes recommendations on testing intervals and the age at which patients should begin regular screening, as both vary widely by the hereditary RCC syndrome in question. While patients with HLRCC should undergo imaging annually,¹⁹¹ those with less aggressive syndromes such as TSC may benefit from testing at longer intervals.²²⁴⁻²²⁶

The age at which patients should begin screening also varies by hereditary RCC syndrome. The panel recommends that patients with confirmed HLRCC, PGL/PCC, TSC, and VHL disease should begin screening in childhood.^{191,224-227} In contrast, those with *BAP1*-TPDS, BHDS, or HPRC should begin screening in adulthood (ie, age 20 years for BHDS, age 30 years for *BAP1*-TPDS and HPRC).^{224,228,229,230} However, the panel notes that if a patient has a known family member with an early diagnosis of hereditary RCC, screening should begin 10 years before the age that the family member was diagnosed, regardless of the syndrome in question.

Genetic Testing and Screening Recommendations for Patients with a Clinical Diagnosis of RCC Who Have Characteristics Consistent with Inherited RCC

The panel includes recommendations for patients who already have a clinical or pathologic diagnosis of RCC and have characteristics potentially associated with a hereditary syndrome (eg, RCC diagnosis at ≤46 years of



NCCN Guidelines Version 2.2024

Kidney Cancer

age, presence of bilateral or multifocal tumors, and/or ≥1 known first- or second-degree relative with RCC). These patients should also undergo genetic risk assessment, and if indicated, genetic testing. The panel also recommends genetic risk evaluation for hereditary RCC syndromes for unaffected individuals who have ≥2 first- or second-degree relatives with RCC (on the same side of the family) and/or any first degree relative with clinical or pathologic diagnosis of a hereditary RCC syndrome who is unable or unwilling to genetically test. If inherited RCC is confirmed, patients should undergo screening as described above, in addition to disease stage-appropriate surveillance.

Kidney-Specific Surgical Recommendations for Patients with a Confirmed Hereditary RCC Syndrome

The panel also provides surgical recommendations for the majority of the included hereditary RCC syndromes, which are based on published data and/or the subcommittee's real-world experience in treating patients with these syndromes. In order to develop these recommendations, they carefully weighed the potential morbidity and mortality of surgical treatment against the potential aggressiveness of each of the syndromes. They agreed that patients with BHDS, HPRC, and TSC may benefit from more conservative treatment, such as nephron-sparing surgery or ablative therapies,^{231,232} while patients with HLRCC should undergo total radical nephrectomy.¹⁹¹ The panel's recommendations for surgical treatment of PGL/PCC vary by tumor size and histology: those with smaller, less aggressive tumors may be eligible for partial nephrectomy, while those with larger, more aggressive tumors (eg, high-grade, sarcomatoid) should undergo radical nephrectomy.²³³ Tumor size also factored into the panel's surgical recommendations for patients with VHL disease; they noted that these patients are likely to undergo multiple surgical resections during their lifetime that may contribute to chronic and progressive renal failure. Thus, the timing of surgical intervention must be carefully determined in order to limit the development of metastases and morbidity associated

with surgical intervention. They agreed that only patients with VHL disease with tumors approaching 3 cm in diameter should undergo partial nephrectomy (or ablative therapy if nephrectomy is contraindicated).^{232,234}

Kidney-Specific Systemic Therapy for Patients with Confirmed Hereditary RCC

The Guidelines include a limited number of kidney-specific systemic therapy recommendations for patients with hereditary RCC. Everolimus was approved in April 2012 for treating TSC-associated benign renal angiomyolipomas not requiring immediate surgery.^{235,236} The panel included it as a category 2A, useful in certain circumstances recommendation for patients with TSC-associated angiomyolipoma.

The panel also included erlotinib/bevacizumab for patients with HLRCC-associated metastatic RCC. While this regimen is not FDA-approved for use in this patient population, its inclusion is supported by clinical trial data showing improved patient outcomes. Erlotinib/bevacizumab treatment led to a 60% ORR and a median PFS of 24.2 months in 20 patients with HLRCC-associated RCC.²³⁷ Based on these data, the panel considers erlotinib/bevacizumab a category 2A, useful in certain circumstances option for patients with HLRCC-associated RCC.

In August 2021, the FDA approved belzutifan for the treatment of patients with VHL disease-associated RCC who require therapy for RCC but do not require immediate surgery.²³⁸ Study-004, an open-label, phase II clinical trial, enrolled 61 patients with VHL-associated RCC; 97% had previously undergone a tumor reduction procedure.²³⁹ The major efficacy endpoint was ORR, which was 49% (95% CI, 36–62) after a median follow-up of 21.8 months with 30 patients confirming PRs. An additional 30 patients (49%) had a best response of SD. Median time to response was 8.2 months. Median duration of response was not reached.²⁴⁰



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024 Kidney Cancer

The panel also considers pazopanib a category 2A, useful in certain circumstances option for patients with VHL disease-associated nonmetastatic lesions. In a phase II trial, pazopanib led to a 42% ORR and a 52% renal tumor-specific response rate in 31 patients with VHL disease.²⁴¹

Data Summary

The following tables summarize the key data supporting the inclusion of systemic therapy regimens for treatment of ccRCC and nccRCC. Table 1 includes data on recommended first-line systemic therapies for patients with ccRCC. Table 2 includes data on recommended subsequent systemic therapies for patients with ccRCC. Table 3 includes data on recommended systemic therapies for patients with nccRCC.

A large, semi-transparent circular graphic is centered on the page. Inside the circle, the word "Discussion" is written in a large, light gray font at the top. Below it, the words "update in progress" are written in a larger, bold, light gray font.



NCCN Guidelines Version 2.2024

Kidney Cancer

Table 1: Key Studies on First-Line Therapy for Patients with Clear Cell RCC (ccRCC)

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	Median PFS (months)	Median OS (months)
Combination Therapy							
JAVELIN Renal 101 Choueiri et al 2020 ¹²³ Motzer et al 2019 ¹²² Note: Only the most recent data are shown.	Axitinib + avelumab	442	Favorable-, intermediate- or poor-risk, systemic therapy-naïve, advanced ccRCC; ECOG PS 0–1 270 patients in the axitinib/avelumab arm and 290 patients in the sunitinib arm were PD-L1+. Data from PD-L1+ patients were reported separately.	19	<u>ORR: Overall population</u> Axi/Ave: 53 (95% CI, 48–57) Sunitinib: 27 (95% CI, 23–32) <u>ORR: PD-L1+</u> Axi/Ave: 56 (95% CI, 50–62) Sunitinib: 27 (95% CI, 22–33) <u>CR (%): Overall population</u> Axi/Ave: 3.8 Sunitinib: 2.0 <u>CR (%): PD-L1+</u> Axi/Ave: 5.6 Sunitinib: 2.4	<u>Overall population</u> Axi/Ave: 13.3 (95% CI, 11.1–15.3) Sunitinib: 8.0 (95% CI, 6.7–9.8) HR, 0.69 (95% CI, 0.57–0.83) $P < .0001$	<u>Overall population</u> Axi/Ave: NE (95% CI, 30–NE) Sunitinib: NE (95% CI, 27.4–NE) HR, 0.80 (95% CI, 0.62–1.03) $P = .0392$
	Sunitinib	444			<u>PD-L1-positive</u> Axi/Ave: 13.8 (95% CI, 10.1–20.7) Sunitinib: 7.0 (95% CI, 5.7–9.6) HR, 0.62 (95% CI, 0.49–0.78) $P < .0001$	<u>PD-L1-positive</u> Axi/Ave: NE (95% CI, NE) Sunitinib: 28.6 (95% CI, 27.4–NE) HR, 0.83 (95% CI, 0.60–1.15) $P = .1301$	
KEYNOTE-426 Rini et al 2019 ¹¹¹ Powels et al 2020 ¹¹²	Axitinib + pembrolizumab	432	Favorable-, intermediate- or poor-risk, systemic therapy-naïve, advanced ccRCC; Karnofsky PS ≥70%	13	Axi/Pem: 59 (95% CI, 55–64) Sunitinib: 36 (95% CI, 31–40) $P < .001$	Axi/Pem: 15.4 (95% CI, 12.7–18.9) Sunitinib: 11.1 (95% CI, 9.1–12.5) HR, 0.71 (95% CI, 0.60–0.84) $P < .0001$	Axi/Pem: Not reached Sunitinib: 35.7 (95% CI, 33.3–[NR]) HR, 0.53 (95% CI, 0.38–0.74) $P < .0001$
	Sunitinib	429					
CheckMate 9ER Choueiri et al 2021 ¹¹⁴	Cabozantinib + nivolumab	323	Favorable-, intermediate- or poor-risk, systemic therapy-naïve, advanced ccRCC; Karnofsky PS ≥70%	18	Cabo/Nivo: 56 Sunitinib: 27 $P < .001$	Cabo/Nivo: 16.6 (95% CI, 12.5–14.9) Sunitinib: 8.3 (95% CI, 7.0–9.7) HR, 0.51 (95% CI, 0.41–0.64) $P < .001$	Cabo/Nivo: NR Sunitinib: NR <u>12-month OS (%)</u> Cabo/Nivo: 86% (95% CI, 81–89) Sunitinib: 76% (95% CI, 71–80) HR, 0.60 (98.89% CI, 0.40–0.89) $P = .001$
	Sunitinib	328					



NCCN Guidelines Version 2.2024

Kidney Cancer

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	Median PFS (months)	Median OS (months)
CheckMate 214 Motzer et al 2018 ¹²⁰	Ipilimumab + nivolumab	550	The study enrolled 425 intermediate-risk, 422 poor-risk, and 249 favorable-risk patients with systemic therapy-naïve, advanced ccRCC; Karnofsky PS ≥70% Note: The study's coprimary endpoints were ORR, OS, and PFS in intermediate- and poor-risk patients. Exploratory analyses of data in favorable-risk patients were reported separately. Combined data for all risk groups are not shown.	67.7	<u>Intermediate-/poor-risk patients</u> <u>ORR</u> Ipi/Nivo: 42 (95% CI, 37–47) Sunitinib: 27 (95% CI, 22–31) $P < .001$ <u>CR (%)</u> Ipi/Nivo: 11 Sunitinib: 2 $P < .001$	Ipi/Nivo: 12.3 <u>HR, 0.72</u> <u>Intermediate-/poor-risk patients</u> Ipi/Nivo: 11.6 (95% CI, 8.4–16.5) Sunitinib: 8.3 (95% CI, 7.0–10.4) <u>HR, 0.73</u> (95% CI, 0.61–0.87)	Ipi/Nivo: 55.7 Sunitinib: 38.4 <u>HR, 0.72</u> (95% CI, 0.62–0.85) <u>Intermediate-/poor-risk patients</u> Ipi/Nivo: 47.0 Sunitinib: 26.6 <u>HR, 0.68</u> (95% CI, 0.58–0.81) $P < .001$
	Sunitinib	546			<u>Favorable-risk patients</u> <u>ORR</u> Ipi/Nivo: 30 (95% CI, 21–38) Sunitinib: 52 (95% CI, 43–61) $P < .001$ <u>CR (%)</u> Ipi/Nivo: 13 Sunitinib: 6	 <u>Favorable-risk patients</u> Ipi/Nivo: 15.3 (95% CI, 9.7–20.3) Sunitinib: 25.1 (95% CI, 20.9–NE) <u>HR, 1.60</u> (95% CI, 1.13–2.26) $P < .001$	Ipi/Nivo: 74.1 Sunitinib: 68.4 <u>HR, 0.94</u> (95% CI, 0.65–1.37)



NCCN Guidelines Version 2.2024

Kidney Cancer

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	Median PFS (months)	Median OS (months)
CLEAR Motzer et al 2021 ¹¹⁸	Lenvatinib + pembrolizumab	355	Favorable-, intermediate-, or poor-risk, systemic therapy-naïve, advanced ccRCC; Karnofsky PS ≥70%	27	<u>ORR</u> Len/Pem: 71 Len/Ev: 54 Sunitinib: 36 <u>ORR, Len/Pem vs. Sunitinib</u> RR: 1.97 (95% CI, 1.69–2.29) <u>ORR, Len/Ev vs. Sunitinib</u> RR: 1.48 (95% CI, 1.26–1.74) <u>CR</u> Len/Pem: 16 Lev/Ev: 10 Sunitinib: 4	Len/Pem: 23.9 (95% CI, 20.8–27.7) Len/Ev: 14.7 (95% CI, 11.1–16.7) Sunitinib: 9.2 (95% CI, 6.0–11.0) <u>Len/Pem vs. Sunitinib</u> HR, 0.66 (95% CI, 0.49–0.88) P = .005 <u>Len/Ev vs. Sunitinib</u> HR, 1.15 (95% CI, 0.88–1.50) P = .30	Len/Pem: NR Len/Ev: NR Sunitinib: NR <u>Len/Pem vs. Sunitinib</u> HR, 0.66 (95% CI, 0.49–0.88) P = .005 <u>Len/Ev vs. Sunitinib</u> HR, 1.15 (95% CI, 0.88–1.50) P = .30
	Lenvatinib + everolimus	357					
	Sunitinib	357					
Monotherapy							
VEG105192 Sternberg et al 2013 ¹²⁷ (OS data) Sternberg et al 2010 ¹²⁶ (PFS and ORR data)	Pazopanib	290	Favorable-, intermediate-, or poor-risk, locally advanced or metastatic ccRCC; ECOG PS 0–1 Note: Of 435 enrolled patients, 202 received prior cytokine treatment and 233 were systemic therapy-naïve. Data were reported separately. See Table 2 for data for patients who received prior treatment.	Median NR; Up to 24 months for primary outcome	Pazopanib: 32 (95% CI, 24–39) Placebo: 4 (95% CI, 0–8) HR, 0.40 (95% CI, 0.27–0.60) P < .0001	Pazopanib: 11.1 Placebo: 2.8 HR, 1.01 (95% CI, 0.72–1.42) P value NR	Pazopanib: 23 Placebo: 24
	Placebo	145					



NCCN Guidelines Version 2.2024

Kidney Cancer

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	Median PFS (months)	Median OS (months)
COMPARZ Motzer et al 2013 ¹²⁸ Note: In 2014, updated OS data were reported in a correspondence letter to the publishing journal. ¹²⁹ Only the most recent OS data are shown.	Pazopanib	557	Favorable- or intermediate-risk, systemic therapy-naïve, advanced or metastatic ccRCC; Karnofsky PS ≥70%	Median NR; Up to 48 months for primary outcome	Pazopanib: 31 Sunitinib: 25 <i>P</i> = .03	Pazopanib: 8.4 (95% CI, 8.3–10.9) Sunitinib: 9.5 (95% CI, 8.3–11.1) HR, 1.05 (95% CI, 0.90–1.22) noninferior	Pazopanib: 28 (95% CI, 26–36) Sunitinib: 29 (95% CI, 25–33) HR, 0.92 (95% CI, 0.79–1.06) <i>P</i> = .24
	Sunitinib	553					
Phase III trial Motzer et al 2007 ¹³⁰	Sunitinib	375	Favorable-, intermediate-, or poor-risk, systemic therapy-naïve, metastatic ccRCC; ECOG PS 0–1	NR	Sunitinib: 31 (95% CI, 26–36) Interferon: 6 (95% CI, 4–9) <i>P</i> < .001	Sunitinib: 11 (95% CI, 10–12) Interferon: 5 (95% CI, 4–6) HR, 0.42 (95% CI, 0.32–0.54) <i>P</i> < .001	Sunitinib: NR Interferon: NR HR, 0.65 (95% CI, 0.45–0.94) <i>P</i> = .02 not significant
	Interferon alfa	375					



NCCN Guidelines Version 2.2024

Kidney Cancer

Table 2: Key Studies on Subsequent Therapy for Patients with Clear Cell RCC (ccRCC)

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
Combination Therapy							
Phase I/II study Apolo et al 2021 ¹⁵⁴ (conference abstract)	Cabozantinib/nivolumab +/- ipilimumab	16	Favorable-, intermediate-, or poor-risk metastatic ccRCC; received at least one line of therapy; Karnofsky PS ≥70%	NR	NR	NR	38.6 (95% CI, 19.4–NE)
CheckMate 016 Hammers et al 2017 ¹⁵⁵ Note: The study also included nivolumab/sunitinib and nivolumab/pazopanib arms, which were discontinued due to high rates of treatment-related AEs. High-dose Ipi/Nivo arm (N = 6) was also included.	Ipilimumab 1 mg/kg /nivolumab 3 mg/kg (N3I1)	47	Favorable-, intermediate-, or poor-risk advanced or metastatic ccRCC; received 0 to ≥4 lines of therapy; Karnofsky PS ≥80% Note: Only the ORR data from treatment-experienced patients were reported separately; OS and PFS outcomes were combined.	22	<u>Treatment-experienced:</u> N3I1: 46 N1I3: 39	<u>All treatment settings:</u> N3I1: 7.7 (95% CI, 3.7–14.3) N1I3: 9.4 (95% CI, 5.6–18.6)	<u>All treatment settings:</u> N3I1: NR (95% CI, 26.7–NR) N1I3: 32.6 (95% CI, 26.0–NR)
	Ipilimumab 3 mg/kg /nivolumab 1 mg/kg (N1I3)	47	22 patients in the N3I1 arm and 26 patients in the N1I3 arm were treatment-experienced.				



NCCN Guidelines Version 2.2024

Kidney Cancer

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
Phase II study Motzer et al 2016 ¹⁴⁹ Motzer et al 2015 ¹⁴⁸	Lenvatinib/everolimus	51	Favorable-, intermediate-, or poor-risk advanced or metastatic ccRCC; received at least one VEGFR-targeted TKI with progression within 9 months of treatment; ECOG PS 0–1	17–19; varied by group	Len/Ev: 43 Ev: 6 Len: 27 <u>Len/Ev vs. Len</u> $P < .0001$	Len/Ev: 14.6 (95% CI, 5.9–20.1) Ev: 5.5 (95% CI, 3.5–7.1) Len: 7.4 (95% CI, 5.6–10.2)	Len/Ev: 25.5 (95% CI, 16.4–NE) Ev: 15.4 (95% CI, 11.8–19.6) Len: 19.1 (95% CI, 13.6–26.2)
	Everolimus	50				<u>Len/Ev vs. Ev</u> HR, 0.40 (95% CI, 0.24–0.68) $P = .0005$	<u>Len/Ev vs. Ev</u> HR, 0.51 (95% CI, 0.30–0.88) $P = .024$
	Lenvatinib	52				<u>Len vs. Ev</u> HR, 0.66 (95% CI, 0.39–1.10) $P = .12$	<u>Len vs. Len/Ev</u> HR, 0.75 (95% CI, 0.43–1.30) $P = .32$
KEYNOTE-146 Lee et al 2021 ¹⁵⁶	Lenvatinib/pembrolizumab, previously treated but ICI-naïve (2+L ICI-naïve)	17	Favorable-, intermediate-, or poor-risk metastatic ccRCC; ECOG PS 0–1	6–51 months; varied by outcome	Week 24 2+L, ICI-naïve: 41 2+L, ICI-TE: 56 TN: 73 <u>Overall</u> 2+L, ICI-naïve: 63 2+L, ICI-TE: 53 TN: 77		
	Lenvatinib/pembrolizumab, ICI treatment-experienced (2+L ICI-TE)	104				2+L, ICI-naïve: 11.8 (95% CI, 5.5–21.9) 2+L, ICI-TE: 12.2 (95% CI, 9.5–17.7) TN: 24.1 (95% CI, 11.7–31.7)	2+L, ICI-naïve: 30.3 (95% CI, 28.7–NR) 2+L, ICI-TE: NR (95% CI, NR–NR) TN: NR (95% CI, 28.6–NR)
	Lenvatinib/pembrolizumab, treatment-naïve (TN)	22					



NCCN Guidelines Version 2.2024

Kidney Cancer

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
Monotherapy							
AXIS Motzer et al 2013 ¹⁵² Rini et al 2011 ¹³⁶ Note: Only the most recent data are shown.	Axitinib	361	Favorable-, intermediate-, or poor-risk, systemic therapy-naïve metastatic ccRCC; ECOG PS 0–1	Up to 36 months	Axi: 19 Sor: 9 <i>P</i> = .0001	Axi: 8.3 (95% CI, 6.7–9.2) Sor: 5.7 (95% CI, 4.7–6.5) HR, 0.67 (95% CI, 0.55–0.78) <i>P</i> < .0001	Axi: 20.1 (95% CI, 16.7–23.4) Sor: 19.2 (95% CI, 17.5–22.3) HR, 0.97 (95% CI, 0.80–1.17) <i>P</i> = .37
	Sorafenib	362					
	METEOR Motzer et al 2018 ¹⁴⁴ Choueiri et al 2016 ¹⁴³ Choueiri et al 2015 ¹⁴² Note: Only the most recent outcome data are shown.	Cabozantinib	330	Favorable-, intermediate-, or poor-risk advanced or metastatic ccRCC; received at least one VEGFR-targeted TKI with progression within 6 months of treatment; Karnofsky PS ≥70%	OS: 22 ¹⁴⁴ ORR, PFS: 19 ¹⁴³	Cabo: 17 Ev: 3 <i>P</i> < .0001	Cabo: 7.4 (95% CI, 6.6–9.1) Ev: 3.9 (95% CI, 3.7–5.1) HR, 0.51 (95% CI, 0.41–0.62) <i>P</i> < .0001
CheckMate 025 Motzer et al 2015 ¹⁵⁰	Nivolumab	406	Nivo: 25 Ev: 5 <i>P</i> < .001			Nivo: 4.6 (95% CI, 3.7–5.4) Ev: 4.4 (95% CI, 3.7–5.5) HR, 0.88 (95% CI, 0.75–1.03) <i>P</i> = .11	Nivo: 25.0 (95% CI, 21.8–NE) Ev: 19.6 (95% CI, 17.6–23.1) HR, 0.73 (95% CI, 0.57–0.93) <i>P</i> = .002
	Everolimus	397					
VEG105192 Sternberg et al 2013 ¹²⁷ (OS data) Sternberg et al 2010 ¹²⁶ (PFS and ORR data)	Pazopanib	290	Favorable-, intermediate-, or poor-risk locally advanced or metastatic ccRCC; ECOG PS 0–1 Note: Of 435 enrolled patients, 202 received prior cytokine treatment and 233 were systemic therapy-naïve. Data were reported separately. See Table 1 for data for patients who were systemic therapy-naïve.	Median NR; Up to 24 months for primary outcome	Paz: 29 Placebo: 3	Paz: 7.4 Placebo: 4.2 HR, 0.54 (95% CI, 0.35–0.84) <i>P</i> < .001	Paz: 23 Placebo: 19 HR, 0.82 (95% CI, 0.57–1.16) <i>P</i> value NR
	Placebo	145					



NCCN Guidelines Version 2.2024

Kidney Cancer

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
TIVO-3 Rini et al 2020 ¹⁶⁵	Tivozanib	175	Favorable-, intermediate-, or poor-risk metastatic ccRCC; received 2–3 prior systemic therapies including at least 1 VEGFR-targeted TKI other than sorafenib or tivozanib; ECOG PS 0–1	19	Tivo: 18 Sor: 8	Tivo: 5.6 (95% CI, 5.3–7.3) Sor: 3.9 (95% CI, 3.7–5.6) HR, 0.73 (95% CI, 0.56–0.94) <i>P</i> = .016	Tivo: 16.4 (95% CI, 13.4–22.2) Sor: 19.7 (95% CI, 15.0–24.2) HR, 0.99 (95% CI, 0.76–1.29) <i>P</i> = .95
	Sorafenib	175					

Table 3: Key Studies on Systemic Therapy for Patients with Non-Clear Cell RCC (nccRCC)

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
Combination Therapy							
Phase II trial Hutson et al 2021 ¹⁸⁴	Lenvatinib/everolimus	31	Unresectable advanced or metastatic nccRCC	NR	PR: 26 SD:58	9.2 (95% CI, 5.5–NE)	15.6 (95% CI, 9.2–NE)
Monotherapy							
Phase 3/4 Checkmate 920 Cohort Tykodi et al 2022 ¹⁹⁹	Nivolumab/ipilimumab	52	Advanced or metastatic nccRCC	24.1	19.6% (CR:4.3%; SD:37%; PD:41.3%)	3.7	21.2 (95% CI, 16.6–NE)
Phase II, Cohort Study Lee et al 2022 ¹⁸⁷	Nivolumab/cabozantinib	47	Advanced nccRCC, underwent 0–1 prior systemic therapies	13.1	47.5% (95% CI, 31.5–63.9)	12.5 (95% CI, 6.3– 16.4)	28 (95% CI, 16.3–NE)
Phase II SWOG 1500 trial Pal et al 2021 ¹⁸⁰	Cabozantinib	46	Favorable-, intermediate-, or poor-risk metastatic papillary RCC; previously received 0– 1 therapies, excluding VEGFR and MET TKIs	NR; up to 36 months follow-up specified in trial	Cabo: 23 Sun: 4 <i>P</i> = .010	Cabo: 9.0 (95% CI, 6–12) Sun: 5.6 (95% CI, 3–7) HR, 0.84 (95% CI, 0.47–1.51)	Cabo: 20.0 Sun: 16.4



NCCN Guidelines Version 2.2024

Kidney Cancer

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
Note: The trial also included savoritinib and crizotinib groups; assignment was halted after a futility analysis.	Sunitinib	44				HR, 0.60 (95% CI, 0.37–0.97) $P = .019$	Not significant
Retrospective study Koshkin et al 2018 ¹⁸⁵	Nivolumab	35	Metastatic nccRCC	9	PR: 20 SD: 29	3.5	NR
Phase II KEYNOTE-427 (cohort B) McDermott et al 2021 ¹⁸⁸	Pembrolizumab	165	Favorable-, intermediate-, or poor-risk, systemic therapy-naïve, newly diagnosed, or recurrent stage IV nccRCC; Karnofsky PS $\geq 70\%$	32	27	4.2 (95% CI, 2.9–5.6)	28.9 (95% CI, 24.3–NE)
Phase II ASPEN trial Armstrong et al 2016 ¹⁸¹	Sunitinib	51	Favorable-, intermediate-, or poor-risk, systemic therapy-naïve metastatic nccRCC (papillary, chromophobe, or unclassified); Karnofsky PS $\geq 60\%$	12–13	Sun: 18 Evero: 9	Sun: 8.3 (80% CI, 5.8–11.4) Evero: 5.6 (80% CI, 5.5–6.0) HR, 1.41 (80% CI, 1.03–1.92) $P = .16$	Sun: 31.5 (95% CI, 14.8–NE) Evero: 13.2 (95% CI, 9.7–37.9) HR, 1.12 (95% CI, 0.7–2.1) $P = .60$
	Everolimus	57					
Phase II ESPN trial Tannir et al 2016 ¹⁸²	Sunitinib	33	Good-, intermediate-, or poor-risk, systemic therapy-naïve metastatic nccRCC (papillary, chromophobe, collecting duct, Xp11.2 translocation, unclassified) or ccRCC with >20% sarcomatoid features; ECOG PS 0–1	24	6	Sun: 6.1 (95% CI, 4.2–9.4) Evero: 4.1 (95% CI, 2.7–10.5) $P = .60$	Sun: 16.2 (95% CI, 14.2–NE) Evero: 14.9 (95% CI, 8.0–23.4) $P = .18$
	Everolimus	35					



NCCN Guidelines Version 2.2024

Kidney Cancer

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021;71:7-33. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33433946>.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35020204>.
3. SEER Cancer Stat Facts: Kidney and Renal Pelvis Cancer. Bethesda, MD: National Cancer Institute; Available at: <http://seer.cancer.gov/statfacts/html/kidrp.html>. Accessed June 28, 2019.
4. Moch H, Gasser T, Amin MB, et al. Prognostic utility of the recently recommended histologic classification and revised TNM staging system of renal cell carcinoma: a Swiss experience with 588 tumors. Cancer 2000;89:604-614. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10931460>.
5. Leibovich BC, Lohse CM, Crispen PL, et al. Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. J Urol 2010;183:1309-1315. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20171681>.
6. Lipworth L, Morgans AK, Edwards TL, et al. Renal cell cancer histological subtype distribution differs by race and sex. BJU Int 2016;117:260-265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25307281>.
7. Eble J, Sauter G, Epstein J, et al. Pathology and genetics of tumours of the urinary system and male genital organs. In: World Health Organization Classification of Tumours. Lyon, France. IARC press; 2004:p. 7.
8. Msaouel P, Hong AL, Mullen EA, et al. Updated recommendations on the diagnosis, management, and clinical trial eligibility criteria for patients with renal medullary carcinoma. Clin Genitourin Cancer 2019;17:1-6. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30287223>.
9. Choyke PL, Glenn GM, Walther MM, et al. Hereditary renal cancers. Radiology 2003;226:33-46. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12511666>.
10. DeVita VT Jr HS, Rosenberg SA. Cancer principles and practice of oncology. (ed 8th). Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
11. Schmidt LS, Linehan WM. Genetic predisposition to kidney cancer. Semin Oncol 2016;43:566-574. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27899189>.
12. DeVita VT Jr LT, Rosenberg SA. DeVita, Hellman, and Rosenberg's Cancer Principles and Practice of Oncology. (ed 10th). Philadelphia, PA: Wolters Kluwer Health; 2015.
13. Howlader N, Noone A, Krapcho M, et al. SEER cancer statistics review, 1975-2014, based on November 2016 SEER data submission, posted to the SEER web site, April 2017: National Cancer Institute. Bethesda, MD; 2017. Available at: https://seer.cancer.gov/csr/1975_2014/.
14. Ficarra V, Schips L, Guille F, et al. Multiinstitutional European validation of the 2002 TNM staging system in conventional and papillary localized renal cell carcinoma. Cancer 2005;104:968-974. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16007683>.
15. Frank I, Blute ML, Leibovich BC, et al. Independent validation of the 2002 American Joint Committee on Cancer primary tumor classification for renal cell carcinoma using a large, single institution cohort. J Urol 2005;173:1889-1892. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15879769>.
16. Zisman A, Pantuck AJ, Chao D, et al. Reevaluation of the 1997 TNM classification for renal cell carcinoma: T1 and T2 cutoff point at 4.5 rather than 7 cm. better correlates with clinical outcome. J Urol 2001;166:54-58. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11435822>.
17. Klatte T, Patard JJ, Goel RH, et al. Prognostic impact of tumor size on pT2 renal cell carcinoma: an international multicenter experience. J Urol



NCCN Guidelines Version 2.2024

Kidney Cancer

2007;178:35-40; discussion 40. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/17521678>.

18. Lam JS, Klatte T, Patard JJ, et al. Prognostic relevance of tumour size in T3a renal cell carcinoma: a multicentre experience. *Eur Urol* 2007;52:155-162. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/17316970>.

19. Minervini A, Lilas L, Minervini R, Selli C. Prognostic value of nuclear grading in patients with intracapsular (pT1-pT2) renal cell carcinoma. Long-term analysis in 213 patients. *Cancer* 2002;94:2590-2595. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12173325>.

20. Dall'Oglio MF, Antunes AA, Sarkis AS, et al. Microvascular tumour invasion in renal cell carcinoma: the most important prognostic factor. *BJU Int* 2007;100:552-555. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/17555475>.

21. Dall'Oglio MF, Ribeiro-Filho LA, Antunes AA, et al. Microvascular tumor invasion, tumor size and Fuhrman grade: a pathological triad for prognostic evaluation of renal cell carcinoma. *J Urol* 2007;178:425-428; discussion 428. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/17561167>.

22. Lam JS, Shvarts O, Said JW, et al. Clinicopathologic and molecular correlations of necrosis in the primary tumor of patients with renal cell carcinoma. *Cancer* 2005;103:2517-2525. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/15880379>.

23. Sengupta S, Lohse CM, Leibovich BC, et al. Histologic coagulative tumor necrosis as a prognostic indicator of renal cell carcinoma aggressiveness. *Cancer* 2005;104:511-520. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/15973740>.

24. Bianchi M, Sun M, Jeldres C, et al. Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. *Ann Oncol* 2012;23:973-980. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/21890909>.

25. Meyer CP, Sun M, Karam JA, et al. Complications after metastasectomy for renal cell carcinoma-a population-based assessment. *Eur Urol* 2017;72:171-174. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/28359734>.

26. Jayson M, Sanders H. Increased incidence of serendipitously discovered renal cell carcinoma. *Urology* 1998;51:203-205. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/9495698>.

27. Luciani LG, Cestari R, Tallarigo C. Incidental renal cell carcinoma-age and stage characterization and clinical implications: study of 1092 patients (1982-1997). *Urology* 2000;56:58-62. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/10869624>.

28. Shuch B, Vourganti S, Ricketts CJ, et al. Defining early-onset kidney cancer: implications for germline and somatic mutation testing and clinical management. *J Clin Oncol* 2014;32:431-437. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/24378414>.

29. Israel GM, Bosniak MA. How I do it: evaluating renal masses. *Radiology* 2005;236:441-450. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/16040900>.

30. Lim DJ, Carter MF. Computerized tomography in the preoperative staging for pulmonary metastases in patients with renal cell carcinoma. *J Urol* 1993;150:1112-1114. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/8371366>.

31. Sheth S, Scatirige JC, Horton KM, et al. Current concepts in the diagnosis and management of renal cell carcinoma: role of multidetector ct and three-dimensional CT. *Radiographics* 2001;21 Spec No:S237-254. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11598260>.

32. Hricak H, Demas BE, Williams RD, et al. Magnetic resonance imaging in the diagnosis and staging of renal and perirenal neoplasms. *Radiology* 1985;154:709-715. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/3969475>.



NCCN Guidelines Version 2.2024

Kidney Cancer

33. Janus CL, Mendelson DS. Comparison of MRI and CT for study of renal and perirenal masses. *Crit Rev Diagn Imaging* 1991;32:69-118. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1863349>.
34. Seaman E, Goluboff ET, Ross S, Sawczuk IS. Association of radionuclide bone scan and serum alkaline phosphatase in patients with metastatic renal cell carcinoma. *Urology* 1996;48:692-695. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8911510>.
35. Shannon BA, Cohen RJ, de Bruto H, Davies RJ. The value of preoperative needle core biopsy for diagnosing benign lesions among small, incidentally detected renal masses. *J Urol* 2008;180:1257-1261; discussion 1261. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18707712>.
36. Park JW, Jo MK, Lee HM. Significance of 18F-fluorodeoxyglucose positron-emission tomography/computed tomography for the postoperative surveillance of advanced renal cell carcinoma. *BJU Int* 2009;103:615-619. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19007371>.
37. Berger A, Brandina R, Atalla MA, et al. Laparoscopic radical nephrectomy for renal cell carcinoma: oncological outcomes at 10 years or more. *J Urol* 2009;182:2172-2176. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19758651>.
38. Burgess NA, Koo BC, Calvert RC, et al. Randomized trial of laparoscopic v open nephrectomy. *J Endourol* 2007;21:610-613. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17638555>.
39. Chung SD, Huang KH, Lai MK, et al. Long-term follow-up of hand-assisted laparoscopic radical nephrectomy for organ-confined renal cell carcinoma. *Urology* 2007;69:652-655. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17445645>.
40. Gabr AH, Gdor Y, Strope SA, et al. Patient and pathologic correlates with perioperative and long-term outcomes of laparoscopic radical nephrectomy. *Urology* 2009;74:635-640. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19616826>.
41. Hemal AK, Kumar A. A prospective comparison of laparoscopic and robotic radical nephrectomy for T1-2N0M0 renal cell carcinoma. *World J Urol* 2009;27:89-94. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18704439>.
42. Hemal AK, Kumar A, Kumar R, et al. Laparoscopic versus open radical nephrectomy for large renal tumors: a long-term prospective comparison. *J Urol* 2007;177:862-866. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17296361>.
43. Luo JH, Zhou FJ, Xie D, et al. Analysis of long-term survival in patients with localized renal cell carcinoma: laparoscopic versus open radical nephrectomy. *World J Urol* 2010;28:289-293. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19916010>.
44. Nambirajan T, Jeschke S, Al-Zahrani H, et al. Prospective, randomized controlled study: transperitoneal laparoscopic versus retroperitoneoscopic radical nephrectomy. *Urology* 2004;64:919-924. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15533478>.
45. Dash A, Vickers AJ, Schachter LR, et al. Comparison of outcomes in elective partial vs radical nephrectomy for clear cell renal cell carcinoma of 4-7 cm. *BJU Int* 2006;97:939-945. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16643474>.
46. Lau WK, Blute ML, Weaver AL, et al. Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. *Mayo Clin Proc* 2000;75:1236-1242. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11126830>.
47. Lee CT, Katz J, Shi W, et al. Surgical management of renal tumors 4 cm. or less in a contemporary cohort. *J Urol* 2000;163:730-736. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10687966>.
48. Leibovich BC, Blute M, Cheville JC, et al. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. *J Urol* 2004;171:1066-1070. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14767272>.



NCCN Guidelines Version 2.2024

Kidney Cancer

49. Zini L, Perrotte P, Capitanio U, et al. Radical versus partial nephrectomy: effect on overall and noncancer mortality. *Cancer* 2009;115:1465-1471. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19195042>.
50. Lee HJ, Liss MA, Derweesh IH. Outcomes of partial nephrectomy for clinical T1b and T2 renal tumors. *Curr Opin Urol* 2014;24:448-452. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24921904>.
51. Huang WC, Levey AS, Serio AM, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol* 2006;7:735-740. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16945768>.
52. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-1305. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15385656>.
53. Thompson RH, Boorjian SA, Lohse CM, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol* 2008;179:468-471; discussion 472-463. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18076931>.
54. Weight CJ, Lieser G, Larson BT, et al. Partial nephrectomy is associated with improved overall survival compared to radical nephrectomy in patients with unanticipated benign renal tumours. *Eur Urol* 2010;58:293-298. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20546991>.
55. Weight CJ, Larson BT, Gao T, et al. Elective partial nephrectomy in patients with clinical T1b renal tumors is associated with improved overall survival. *Urology* 2010;76:631-637. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20451967>.
56. Kim SP, Thompson RH, Boorjian SA, et al. Comparative effectiveness for survival and renal function of partial and radical nephrectomy for localized renal tumors: a systematic review and meta-analysis. *J Urol* 2012;188:51-57. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22591957>.
57. Thompson RH, Siddiqui S, Lohse CM, et al. Partial versus radical nephrectomy for 4 to 7 cm renal cortical tumors. *J Urol* 2009;182:2601-2606. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19836797>.
58. Hollingsworth JM, Miller DC, Dunn RL, et al. Surgical management of low-stage renal cell carcinoma: Technology does not supersede biology. *Urology* 2006;67:1175-1180. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16765177>.
59. Shuch B, Lam JS, Belldegrun AS. Open partial nephrectomy for the treatment of renal cell carcinoma. *Curr Urol Rep* 2006;7:31-38. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16480666>.
60. Chen DY, Uzzo RG. Optimal management of localized renal cell carcinoma: surgery, ablation, or active surveillance. *J Natl Compr Canc Netw* 2009;7:635-642; quiz 643. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19555585>.
61. Tan HJ, Norton EC, Ye Z, et al. Long-term survival following partial vs radical nephrectomy among older patients with early-stage kidney cancer. *JAMA* 2012;307:1629-1635. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22511691>.
62. Gill IS, Kavoussi LR, Lane BR, et al. Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumors. *J Urol* 2007;178:41-46. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17574056>.
63. Gong EM, Orvieto MA, Zorn KC, et al. Comparison of laparoscopic and open partial nephrectomy in clinical T1a renal tumors. *J Endourol* 2008;22:953-957. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18363510>.
64. Lane BR, Gill IS. 7-year oncological outcomes after laparoscopic and open partial nephrectomy. *J Urol* 2010;183:473-479. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20006866>.



NCCN Guidelines Version 2.2024

Kidney Cancer

65. Funahashi Y, Hattori R, Yamamoto T, et al. Ischemic renal damage after nephron-sparing surgery in patients with normal contralateral kidney. *Eur Urol* 2009;55:209-215. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18706758>.
66. Blom JH, van Poppel H, Marechal JM, et al. Radical nephrectomy with and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. *Eur Urol* 2009;55:28-34. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18848382>.
67. Blute ML, Leibovich BC, Cheville JC, et al. A protocol for performing extended lymph node dissection using primary tumor pathological features for patients treated with radical nephrectomy for clear cell renal cell carcinoma. *J Urol* 2004;172:465-469. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15247704>.
68. Capitanio U, Becker F, Blute ML, et al. Lymph node dissection in renal cell carcinoma. *Eur Urol* 2011;60:1212-1220. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21940096>.
69. Shi X, Feng D, Li D, et al. The role of lymph node dissection for non-metastatic renal cell carcinoma: An updated systematic review and meta-analysis. *Front Oncol* 2021;11:790381. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35096589>.
70. Kuczyk M, Munch T, Machtens S, et al. The need for routine adrenalectomy during surgical treatment for renal cell cancer: the Hannover experience. *BJU Int* 2002;89:517-522. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11942955>.
71. Kuczyk M, Wegener G, Jonas U. The therapeutic value of adrenalectomy in case of solitary metastatic spread originating from primary renal cell cancer. *Eur Urol* 2005;48:252-257. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15936136>.
72. O'Malley RL, Godoy G, Kanofsky JA, Taneja SS. The necessity of adrenalectomy at the time of radical nephrectomy: a systematic review. *J Urol* 2009;181:209-217. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19286216>.
73. Lane BR, Tiong HY, Campbell SC, et al. Management of the adrenal gland during partial nephrectomy. *J Urol* 2009;181:2430-2436; discussion 2436-2437. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19371896>.
74. Rais-Bahrami S, Guzzo TJ, Jarrett TW, et al. Incidentally discovered renal masses: oncological and perioperative outcomes in patients with delayed surgical intervention. *BJU Int* 2009;103:1355-1358. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19239459>.
75. Abouassaly R, Lane BR, Novick AC. Active surveillance of renal masses in elderly patients. *J Urol* 2008;180:505-508; discussion 508-509. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18550113>.
76. Lane BR, Abouassaly R, Gao T, et al. Active treatment of localized renal tumors may not impact overall survival in patients aged 75 years or older. *Cancer* 2010;116:3119-3126. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20564627>.
77. Campbell S, Uzzo RG, Allaf ME, et al. Renal mass and localized renal cancer: AUA guideline. *J Urol* 2017;198:520-529. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28479239>.
78. Pierorazio PM, Johnson MH, Patel HD, et al. Management of renal masses and localized renal cancer: Systematic review and meta-analysis. *J Urol* 2016;196:989-999. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27157369>.
79. Chan VW, Abul A, Osman FH, et al. Ablative therapies versus partial nephrectomy for small renal masses - A systematic review and meta-analysis. *Int J Surg* 2022;97:106194. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34958968>.
80. Simmons MN, Weight CJ, Gill IS. Laparoscopic radical versus partial nephrectomy for tumors >4 cm: intermediate-term oncologic and functional outcomes. *Urology* 2009;73:1077-1082. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19394509>.



NCCN Guidelines Version 2.2024

Kidney Cancer

81. Peycelon M, Hupertan V, Comperat E, et al. Long-term outcomes after nephron sparing surgery for renal cell carcinoma larger than 4 cm. *J Urol* 2009;181:35-41. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19012929>.
82. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet* 2016;387:2008-2016. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26969090>.
83. Motzer RJ, Haas NB, Donskov F, et al. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with locally advanced renal cell carcinoma (RCC) (PROTECT). *Journal of Clinical Oncology* 2017;35:4507-4507. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.4507.
84. Gross-Goupil M, Kwon TG, Eto M, et al. Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. *Ann Oncol* 2018;29:2371-2378. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30346481>.
85. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med* 2016;375:2246-2254. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27718781>.
86. Motzer RJ, Ravaud A, Patard JJ, et al. Adjuvant sunitinib for high-risk renal cell carcinoma after nephrectomy: Subgroup analyses and updated overall survival results. *Eur Urol* 2018;73:62-68. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28967554>.
87. Riaz IB, Siddiqi R, Islam M, et al. Adjuvant tyrosine kinase inhibitors in renal cell carcinoma: A concluded living systematic review and meta-analysis. *JCO Clin Cancer Inform* 2021;5:588-599. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34043431>.
88. Laukhtina E, Quhal F, Mori K, et al. Adjuvant therapy with tyrosine kinase inhibitors for localized and locally advanced renal cell carcinoma: an updated systematic review and meta-analysis. *Urol Oncol* 2021;39:764-773. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34400065>.
89. Choueiri TK, Tomczak P, Park SH, et al. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. *N Engl J Med* 2021;385:683-694. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34407342>.
90. Eggener SE, Yossepowitch O, Pettus JA, et al. Renal cell carcinoma recurrence after nephrectomy for localized disease: predicting survival from time of recurrence. *J Clin Oncol* 2006;24:3101-3106. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16809736>.
91. Stewart SB, Thompson RH, Psutka SP, et al. Evaluation of the National Comprehensive Cancer Network and American Urological Association renal cell carcinoma surveillance guidelines. *J Clin Oncol* 2014;32:4059-4065. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25403213>.
92. Dabestani S, Beisland C, Stewart GD, et al. Long-term outcomes of follow-up for initially localised clear cell renal cell carcinoma: RECUR database analysis. *Eur Urol Focus* 2019;5:857-866. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29525381>.
93. Mucksavage P, Kutikov A, Magerfleisch L, et al. Comparison of radiographical imaging modalities for measuring the diameter of renal masses: is there a sizeable difference? *BJU Int* 2011;108:E232-236. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21348913>.
94. Herr HW. Partial nephrectomy for incidental renal cell carcinoma. *Br J Urol* 1994;74:431-433. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7820418>.
95. Morgan WR, Zincke H. Progression and survival after renal-conserving surgery for renal cell carcinoma: experience in 104 patients and extended followup. *J Urol* 1990;144:852-857; discussion 857-858. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2398558>.
96. Lam JS, Shvarts O, Leppert JT, et al. Postoperative surveillance protocol for patients with localized and locally advanced renal cell



NCCN Guidelines Version 2.2024

Kidney Cancer

carcinoma based on a validated prognostic nomogram and risk group stratification system. *J Urol* 2005;174:466-472; discussion 472; quiz 801. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16006866>.

97. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 2002;20:289-296. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11773181>.

98. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009;27:5794-5799. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19826129>.

99. Mekhail TM, Abou-Jawde RM, Boumerhi G, et al. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. *J Clin Oncol* 2005;23:832-841. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15681528>.

100. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *Lancet Oncol* 2013;14:141-148. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23312463>.

101. Culp SH, Tannir NM, Abel EJ, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? *Cancer* 2010;116:3378-3388. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20564061>.

102. Choueiri TK, Xie W, Kollmannsberger C, et al. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. *J Urol* 2011;185:60-66. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21074201>.

103. Mejean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. *N Engl J Med* 2018;379:417-427. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29860937>.

104. Motzer RJ, Russo P. Cytoreductive nephrectomy - patient selection is key. *N Engl J Med* 2018;379:481-482. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29860908>.

105. Mejean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy for patients with metastatic renal cell carcinoma: Is there still a role for cytoreductive nephrectomy? *Eur Urol* 2021;80:417-424. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34187771>.

106. Siva S, Ellis RJ, Ponsky L, et al. Consensus statement from the International Radiosurgery Oncology Consortium for Kidney for primary renal cell carcinoma. *Future Oncol* 2016;12:637-645. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26837701>.

107. Siva S, Louie AV, Warner A, et al. Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). *Cancer* 2018;124:934-942. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29266183>.

108. Meyer E, Pasquier D, Bernadou G, et al. Stereotactic radiation therapy in the strategy of treatment of metastatic renal cell carcinoma: A study of the Getug group. *Eur J Cancer* 2018;98:38-47. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29864737>.

109. FDA approves pembrolizumab plus axitinib for advanced renal cell carcinoma. Available at: <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-plus-axitinib-advanced-renal-cell-carcinoma>. Accessed December 20, 2021.

110. Pembrolizumab (KEYTRUDA) prescribing information. Available at: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.



NCCN Guidelines Version 2.2024

Kidney Cancer

111. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019;380:1116-1127. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30779529>.
112. Powles T, Plimack ER, Soulieres D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2020;21:1563-1573. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33284113>.
113. FDA approves nivolumab plus cabozantinib for advanced renal cell carcinoma. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-plus-cabozantinib-advanced-renal-cell-carcinoma>. Accessed December 20, 2021.
114. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2021;384:829-841. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33657295>.
115. Motzer RJ, Choueiri TK, Powles T, et al. Nivolumab + cabozantinib (NIVO+CABO) versus sunitinib (SUN) for advanced renal cell carcinoma (aRCC): Outcomes by sarcomatoid histology and updated trial results with extended follow-up of CheckMate 9ER. *Journal of Clinical Oncology* 2021;39:308-308. Available at: https://doi.org/10.1200/JCO.2021.39.6_suppl.308.
116. Cella D, Motzer RJ, Suarez C, et al. Patient-reported outcomes with first-line nivolumab plus cabozantinib versus sunitinib in patients with advanced renal cell carcinoma treated in CheckMate 9ER: an open-label, randomised, phase 3 trial. *Lancet Oncol* 2022;23:292-303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35032437>.
117. FDA approves lenvatinib plus pembrolizumab for advanced renal cell carcinoma. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-levatinib-plus-pembrolizumab-advanced-renal-cell-carcinoma>. Accessed December 20, 2021.
118. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med* 2021;384:1289-1300. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33616314>.
119. FDA approves nivolumab plus ipilimumab combination for intermediate or poor-risk advanced renal cell carcinoma. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-plus-ipilimumab-combination-intermediate-or-poor-risk-advanced-renal-cell>. Accessed December 20, 2021.
120. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018;378:1277-1290. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29562145>.
121. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the alliance A031203 CABOSUN trial. *J Clin Oncol* 2017;35:591-597. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28199818>.
122. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019;380:1103-1115. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30779531>.
123. Choueiri TK, Motzer RJ, Rini BI, et al. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. *Ann Oncol* 2020;31:1030-1039. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32339648>.
124. Choueiri TK, Larkin J, Pal S, et al. Efficacy and correlative analyses of avelumab plus axitinib versus sunitinib in sarcomatoid renal cell carcinoma: post hoc analysis of a randomized clinical trial. *ESMO Open* 2021;6:100101. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33901870>.



NCCN Guidelines Version 2.2024

Kidney Cancer

125. Quhal F, Mori K, Fajkovic H, et al. Immunotherapy-based combinations in the first-line treatment of metastatic renal cell carcinoma with sarcomatoid features: a systematic review and network meta-analysis. *Curr Opin Urol* 2022;32:61-68. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34720102>.
126. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010;28:1061-1068. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20100962>.
127. Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. *Eur J Cancer* 2013;49:1287-1296. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23321547>.
128. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 2013;369:722-731. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23964934>.
129. Motzer RJ, Hutson TE, McCann L, et al. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. *N Engl J Med* 2014;370:1769-1770. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24785224>.
130. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356:115-124. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17215529>.
131. Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006;24:16-24. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16330672>.
132. Chow LQ, Eckhardt SG. Sunitinib: from rational design to clinical efficacy. *J Clin Oncol* 2007;25:884-896. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17327610>.
133. Faivre S, Delbaldo C, Vera K, et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol* 2006;24:25-35. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16314617>.
134. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:3584-3590. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19487381>.
135. Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. *Lancet Oncol* 2016;17:1317-1324. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27498080>.
136. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011;378:1931-1939. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22056247>.
137. Hutson TE, Lesovoy V, Al-Shukri S, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. *Lancet Oncol* 2013;14:1287-1294. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24206640>.
138. McDermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2005;23:133-141. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15625368>.
139. Rosenberg SA, Mule JJ, Spiess PJ, et al. Regression of established pulmonary metastases and subcutaneous tumor mediated by the systemic administration of high-dose recombinant interleukin 2. *J Exp Med* 1985;161:1169-1188. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3886826>.
140. Yang JC, Sherry RM, Steinberg SM, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. *J*



NCCN Guidelines Version 2.2024

Kidney Cancer

Clin Oncol 2003;21:3127-3132. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/12915604>.

141. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-2281. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17538086>.

142. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1814-1823. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26406150>.

143. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 2016;17:917-927. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27279544>.

144. Motzer RJ, Escudier B, Powles T, et al. Long-term follow-up of overall survival for cabozantinib versus everolimus in advanced renal cell carcinoma. Br J Cancer 2018;118:1176-1178. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/29576624>.

145. Amzal B, Fu S, Meng J, et al. Cabozantinib versus everolimus, nivolumab, axitinib, sorafenib and best supportive care: A network meta-analysis of progression-free survival and overall survival in second line treatment of advanced renal cell carcinoma. PLoS One 2017;12:e0184423. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28886175>.

146. Lenvatinib (LENVIMA) prescribing information. Available at:
<http://www.lenvima.com/pdfs/prescribing-information.pdf>.

147. FDA approves lenvatinib in combination with everolimus for advanced renal cell carcinoma. Available at:
<https://www.fda.gov/drugs/resources-information-approved-drugs/lenvatinib-combination-everolimus>. Accessed December 20, 2021.

148. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol 2015;16:1473-1482. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26482279>.

149. Motzer RJ, Hutson TE, Ren M, et al. Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. Lancet Oncol 2016;17:e4-5. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26758760>.

150. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803-1813. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26406148>.

151. Escudier B, Sharma P, McDermott DF, et al. CheckMate 025 randomized phase 3 study: Outcomes by key baseline factors and prior therapy for nivolumab versus everolimus in advanced renal cell carcinoma. Eur Urol 2017;72:962-971. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28262413>.

152. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol 2013;14:552-562. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23598172>.

153. Apolo AB, Nadal R, Girardi DM, et al. Phase I study of cabozantinib and nivolumab alone or with ipilimumab for advanced or metastatic urothelial carcinoma and other genitourinary tumors. J Clin Oncol 2020;38:3672-3684. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32915679>.

154. Final results from a phase I trial and expansion cohorts of cabozantinib and nivolumab (CaboNivo) alone or with ipilimumab (CaboNivoli) for metastatic genitourinary tumors. ASCO; 2021. Available at: <https://meetinglibrary.asco.org/record/194730/abstract>. Accessed



NCCN Guidelines Version 2.2024

Kidney Cancer

155. Hammers HJ, Plimack ER, Infante JR, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: The Checkmate 016 study. *J Clin Oncol* 2017;35:3851-3858. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28678668>.
156. Lee CH, Shah AY, Rasco D, et al. Lenvatinib plus pembrolizumab in patients with either treatment-naive or previously treated metastatic renal cell carcinoma (Study 111/KEYNOTE-146): a phase 1b/2 study. *Lancet Oncol* 2021;22:946-958. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34143969>.
157. Hainsworth JD, Rubin MS, Arrowsmith ER, et al. Pazopanib as second-line treatment after sunitinib or bevacizumab in patients with advanced renal cell carcinoma: a Sarah Cannon Oncology Research Consortium Phase II Trial. *Clin Genitourin Cancer* 2013;11:270-275. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23665131>.
158. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006;295:2516-2524. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16757724>.
159. Dudek AZ, Zolnierek J, Dham A, et al. Sequential therapy with sorafenib and sunitinib in renal cell carcinoma. *Cancer* 2009;115:61-67. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19051290>.
160. Eichelberg C, Heuer R, Chun FK, et al. Sequential use of the tyrosine kinase inhibitors sorafenib and sunitinib in metastatic renal cell carcinoma: a retrospective outcome analysis. *Eur Urol* 2008;54:1373-1378. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18692304>.
161. Sablin MP, Negrier S, Ravaud A, et al. Sequential sorafenib and sunitinib for renal cell carcinoma. *J Urol* 2009;182:29-34; discussion 34. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19447417>.
162. Zimmermann K, Schmittel A, Steiner U, et al. Sunitinib treatment for patients with advanced clear-cell renal-cell carcinoma after progression on sorafenib. *Oncology* 2009;76:350-354. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19321976>.
163. Garcia JA, Hutson TE, Elson P, et al. Sorafenib in patients with metastatic renal cell carcinoma refractory to either sunitinib or bevacizumab. *Cancer* 2010;116:5383-5390. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20806321>.
164. FDA approves tivozanib for relapsed or refractory advanced renal cell carcinoma. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tivozanib-relapsed-or-refractory-advanced-renal-cell-carcinoma>. Accessed December 20, 2021.
165. Rini BI, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. *Lancet Oncol* 2020;21:95-104. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31810797>.
166. Szarek M, Needle MN, Rini BI, et al. Q-TWiST Analysis of Tivozanib Versus Sorafenib in Patients With Advanced Renal Cell Carcinoma in the TIVO-3 Study. *Clin Genitourin Cancer* 2021;19:e461-468 e465. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33980467>.
167. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008;372:449-456. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18653228>.
168. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. *Cancer* 2010;116:4256-4265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20549832>.
169. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;349:427-434. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12890841>.
170. Awada A, Hendlisz A, Gil T, et al. Phase I safety and pharmacokinetics of BAY 43-9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumours. *Br J Cancer*



NCCN Guidelines Version 2.2024

Kidney Cancer

2005;92:1855-1861. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15870716>.

171. Clark JW, Eder JP, Ryan D, et al. Safety and pharmacokinetics of the dual action Raf kinase and vascular endothelial growth factor receptor inhibitor, BAY 43-9006, in patients with advanced, refractory solid tumors. Clin Cancer Res 2005;11:5472-5480. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/16061863>.

172. Moore M, Hirte HW, Siu L, et al. Phase I study to determine the safety and pharmacokinetics of the novel Raf kinase and VEGFR inhibitor BAY 43-9006, administered for 28 days on/7 days off in patients with advanced, refractory solid tumors. Ann Oncol 2005;16:1688-1694. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16006586>.

173. Strumberg D, Richly H, Hilger RA, et al. Phase I clinical and pharmacokinetic study of the Novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. J Clin Oncol 2005;23:965-972. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/15613696>.

174. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004;64:7099-7109. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/15466206>.

175. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125-134. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/17215530>.

176. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009;27:3312-3318. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/19451442>.

177. Hutson TE, Escudier B, Esteban E, et al. Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in

patients with metastatic renal cell carcinoma. J Clin Oncol 2014;32:760-767. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24297950>.

178. Bauer TM, Choueiri TK, Papadopoulos KP, et al. The oral HIF-2 α inhibitor MK-6482 in patients with advanced clear cell renal cell carcinoma (RCC): Updated follow-up of a phase I/II study. Journal of Clinical Oncology 2021;39:273-273. Available at:
https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.6_suppl.273.

179. de Velasco G, McKay RR, Lin X, et al. Comprehensive analysis of survival outcomes in non-clear cell renal cell carcinoma patients treated in clinical trials. Clin Genitourin Cancer 2017;15:652-660 e651. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/28410911>.

180. Pal SK, Tangen C, Thompson IM, Jr., et al. A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial. Lancet 2021;397:695-703. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/33592176>.

181. Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. Lancet Oncol 2016;17:378-388. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/26794930>.

182. Tannir NM, Jonasch E, Albiges L, et al. Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (ESPN): a randomized multicenter phase 2 trial. Eur Urol 2016;69:866-874. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26626617>.

183. Ciccarese C, Iacovelli R, Brunelli M, et al. Addressing the best treatment for non-clear cell renal cell carcinoma: A meta-analysis of randomised clinical trials comparing VEGFR-TKIs versus mTORi-targeted therapies. Eur J Cancer 2017;83:237-246. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/28756136>.

184. Hutson TE, Michaelson MD, Kuzel TM, et al. A single-arm, multicenter, phase 2 study of lenvatinib plus everolimus in patients with



NCCN Guidelines Version 2.2024

Kidney Cancer

advanced non-clear cell renal cell carcinoma. Eur Urol 2021;80:162-170. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33867192>.

185. Koshkin VS, Barata PC, Zhang T, et al. Clinical activity of nivolumab in patients with non-clear cell renal cell carcinoma. J Immunother Cancer 2018;6:9. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29378660>.

186. McKay RR, Bosse D, Xie W, et al. The clinical activity of PD-1/PD-L1 inhibitors in metastatic non-clear cell renal cell carcinoma. Cancer Immunol Res 2018;6:758-765. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29748390>.

187. Lee CH, Voss MH, Carlo MI, et al. Phase II trial of cabozantinib plus nivolumab in patients with non-clear-cell renal cell carcinoma and genomic correlates. J Clin Oncol 2022;0:JCO2101944. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35298296>.

188. McDermott DF, Lee JL, Ziobro M, et al. Open-label, single-arm, phase ii study of pembrolizumab monotherapy as first-line therapy in patients with advanced non-clear cell renal cell carcinoma. J Clin Oncol 2021;39:1029-1039. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33529058>.

189. Park I, Lee SH, Lee JL. A multicenter phase II trial of axitinib in patients with recurrent or metastatic non-clear-cell renal cell carcinoma who had failed prior treatment with temsirolimus. Clin Genitourin Cancer 2018;16:e997-e1002. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29903415>.

190. Irshad T, Olencki T, Zynger DL, et al. Bevacizumab in metastatic papillary renal cell carcinoma (PRCC). ASCO Meeting Abstracts 2011;29:e15158. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2011.29.15_suppl.e15158.

191. Menko FH, Maher ER, Schmidt LS, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. Fam Cancer 2014;13:637-644. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25012257>.

192. Srinivasan R, Gurram S, Al Harthy M, et al. Results from a phase II study of bevacizumab and erlotinib in subjects with advanced hereditary leiomyomatosis and renal cell cancer (HLRCC) or sporadic papillary renal cell cancer. Journal of Clinical Oncology 2020;38:5004-5004. Available at: https://doi.org/10.1200/JCO.2020.38.15_suppl.5004.

193. Voss MH, Molina AM, Chen YB, et al. Phase II trial and correlative genomic analysis of everolimus plus bevacizumab in advanced non-clear cell renal cell carcinoma. J Clin Oncol 2016;34:3846-3853. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27601542>.

194. Buti S, Bersanelli M, Maines F, et al. First-line pazopanib in non-clear-cell renal carcinoma: The italian retrospective multicenter PANORAMA study. Clin Genitourin Cancer 2017;15:e609-e614. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28108284>.

195. Gordon MS, Hussey M, Nagle RB, et al. Phase II study of erlotinib in patients with locally advanced or metastatic papillary histology renal cell cancer: SWOG S0317. J Clin Oncol 2009;27:5788-5793. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19884559>.

196. Blank CU, Bono P, Larkin JMG, et al. Safety and efficacy of everolimus in patients with non-clear cell renal cell carcinoma refractory to VEGF-targeted therapy: Subgroup analysis of REACT [abstract]. J Clin Oncol 2012;30 (5_suppl):Abstract 402. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2012.30.5_suppl.402.

197. Koh Y, Lim HY, Ahn JH, et al. Phase II trial of everolimus for the treatment of nonclear-cell renal cell carcinoma. Ann Oncol 2013;24:1026-1031. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23180114>.

198. Escudier B, Molinie V, Bracarda S, et al. Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis. Eur J Cancer 2016;69:226-235. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27680407>.

199. Tykodi SS, Gordan LN, Alter RS, et al. Safety and efficacy of nivolumab plus ipilimumab in patients with advanced non-clear cell renal cell carcinoma: results from the phase 3b/4 CheckMate 920 trial. J



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024

Kidney Cancer

Immunother Cancer 2022;10. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/35210307>.

200. Jung KS, Lee SJ, Park SH, et al. Pazopanib for the treatment of non-clear cell renal cell carcinoma: A single-arm, open-label, multicenter, phase II study. *Cancer Res Treat* 2018;50:488-494. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28546525>.

201. A phase II efficacy trial of pazopanib in non-clear cell metastatic renal cell cancer (mRCC) PINCR (Clinical Trial ID: NCT01767636. Available at: <https://clinicaltrials.gov/ct2/show/NCT01767636>.

202. Dutcher JP, de Souza P, McDermott D, et al. Effect of temsirolimus versus interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumor histologies. *Med Oncol* 2009;26:202-209. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19229667>.

203. Venugopal B, Ansari J, Aitchison M, et al. Efficacy of temsirolimus in metastatic chromophobe renal cell carcinoma. *BMC Urol* 2013;13:26. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23688003>.

204. Hakimi AA, Koi PT, Milhoua PM, et al. Renal medullary carcinoma: the Bronx experience. *Urology* 2007;70:878-882. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18068443>.

205. Watanabe IC, Billis A, Guimaraes MS, et al. Renal medullary carcinoma: report of seven cases from Brazil. *Mod Pathol* 2007;20:914-920. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17643096>.

206. Shah AY, Karam JA, Malouf GG, et al. Management and outcomes of patients with renal medullary carcinoma: a multicentre collaborative study. *BJU Int* 2017;120:782-792. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27860149>.

207. Srigley JR, Delahunt B. Uncommon and recently described renal carcinomas. *Mod Pathol* 2009;22 Suppl 2:S2-S23. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19494850>.

208. Tokuda N, Naito S, Matsuzaki O, et al. Collecting duct (Bellini duct) renal cell carcinoma: a nationwide survey in Japan. *J Urol* 2006;176:40-43; discussion 43. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16753362>.

209. Karakiewicz PI, Trinh QD, Rioux-Leclercq N, et al. Collecting duct renal cell carcinoma: a matched analysis of 41 cases. *Eur Urol* 2007;52:1140-1145. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17336449>.

210. Gupta R, Billis A, Shah RB, et al. Carcinoma of the collecting ducts of Bellini and renal medullary carcinoma: clinicopathologic analysis of 52 cases of rare aggressive subtypes of renal cell carcinoma with a focus on their interrelationship. *Am J Surg Pathol* 2012;36:1265-1278. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22895263>.

211. Oudard S, Banu E, Vieillefond A, et al. Prospective multicenter phase II study of gemcitabine plus platinum salt for metastatic collecting duct carcinoma: results of a GETUG (Groupe d'Etudes des Tumeurs Uro-Genitales) study. *J Urol* 2007;177:1698-1702. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17437788>.

212. Wilson NR, Wiele AJ, Surasi DS, et al. Efficacy and safety of gemcitabine plus doxorubicin in patients with renal medullary carcinoma. *Clin Genitourin Cancer* 2021;19:e401-e408. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34625389>.

213. Roubaud G, Gross-Gouip M, Wallerand H, et al. Combination of gemcitabine and doxorubicin in rapidly progressive metastatic renal cell carcinoma and/or sarcomatoid renal cell carcinoma. *Oncology* 2011;80:214-218. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21720184>.

214. Fokas E, Henzel M, Hamm K, et al. Radiotherapy for brain metastases from renal cell cancer: should whole-brain radiotherapy be added to stereotactic radiosurgery?: analysis of 88 patients. *Strahlenther Onkol* 2010;186:210-217. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20165820>.



NCCN Guidelines Version 2.2024

Kidney Cancer

215. Zekri J, Ahmed N, Coleman RE, Hancock BW. The skeletal metastatic complications of renal cell carcinoma. *Int J Oncol* 2001;19:379-382. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11445855>.
216. Schlesinger-Raab A, Treiber U, Zaak D, et al. Metastatic renal cell carcinoma: results of a population-based study with 25 years follow-up. *Eur J Cancer* 2008;44:2485-2495. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18783939>.
217. Roza T, Hakim L, van Poppel H, Joniau S. Bone-targeted therapies for elderly patients with renal cell carcinoma: current and future directions. *Drugs Aging* 2013;30:877-886. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24072355>.
218. Hunter GK, Balagamwala EH, Koyfman SA, et al. The efficacy of external beam radiotherapy and stereotactic body radiotherapy for painful spinal metastases from renal cell carcinoma. *Pract Radiat Oncol* 2012;2:e95-e100. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24674192>.
219. Zelefsky MJ, Greco C, Motzer R, et al. Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. *Int J Radiat Oncol Biol Phys* 2012;82:1744-1748. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21596489>.
220. Lipton A, Zheng M, Seaman J. Zoledronic acid delays the onset of skeletal-related events and progression of skeletal disease in patients with advanced renal cell carcinoma. *Cancer* 2003;98:962-969. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12942563>.
221. Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. *Cancer* 2004;100:2613-2621. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15197804>.
222. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* 2011;29:1125-1132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21343556>.
223. Maher ER. Hereditary renal cell carcinoma syndromes: diagnosis, surveillance and management. *World J Urol* 2018;36:1891-1898. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29680948>.
224. Rednam SP, Erez A, Druker H, et al. Von hippel-lindau and hereditary pheochromocytoma/paraganglioma syndromes: Clinical features, genetics, and surveillance recommendations in childhood. *Clin Cancer Res* 2017;23:e68-e75. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28620007>.
225. Tufton N, Sahdev A, Akker SA. Radiological surveillance screening in asymptomatic succinate dehydrogenase mutation carriers. *J Endocr Soc* 2017;1:897-907. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29264540>.
226. Eijkelenkamp K, Osinga TE, de Jong MM, et al. Calculating the optimal surveillance for head and neck paraganglioma in SDHB-mutation carriers. *Fam Cancer* 2017;16:123-130. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27573198>.
227. Krueger DA, Northrup H, International Tuberous Sclerosis Complex Consensus G. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol* 2013;49:255-265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24053983>.
228. Menko FH, van Steensel MA, Giraud S, et al. Birt-Hogg-Dube syndrome: diagnosis and management. *Lancet Oncol* 2009;10:1199-1206. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19959076>.
229. Star P, Goodwin A, Kapoor R, et al. Germline BAP1-positive patients: the dilemmas of cancer surveillance and a proposed interdisciplinary



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024 Kidney Cancer

- consensus monitoring strategy. Eur J Cancer 2018;92:48-53. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29413689>.
230. Ornstein DK, Lubensky IA, Venzon D, et al. Prevalence of microscopic tumors in normal appearing renal parenchyma of patients with hereditary papillary renal cancer. J Urol 2000;163:431-433. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10647647>.
231. Pavlovich CP, Grubb RL, 3rd, Hurley K, et al. Evaluation and management of renal tumors in the Birt-Hogg-Dube syndrome. J Urol 2005;173:1482-1486. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15821464>.
232. Shuch B, Singer EA, Bratslavsky G. The surgical approach to multifocal renal cancers: hereditary syndromes, ipsilateral multifocality, and bilateral tumors. Urol Clin North Am 2012;39:133-148, v. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22487757>.
233. Gill AJ, Hes O, Papathomas T, et al. Succinate dehydrogenase (SDH)-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients. Am J Surg Pathol 2014;38:1588-1602. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25025441>.
234. Singer EA, Vourganti S, Lin KY, et al. Outcomes of patients with surgically treated bilateral renal masses and a minimum of 10 years of followup. J Urol 2012;188:2084-2088. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23083858>.
235. Everolimus (AFINITOR) Prescribing Information. Available at: <https://www.novartis.us/sites/www.novartis.us/files/afinitor.pdf>. Accessed
236. Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2013;381:817-824. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23312829>.
237. Srinivasan R, Su D, Stamatakis L, et al. Mechanism based targeted therapy for hereditary leiomyomatosis and renal cell cancer (HLRCC) and sporadic papillary renal cell carcinoma: interim results from a phase 2 study of bevacizumab and erlotinib [abstract]. Eur J Cancer 2014;50:8. Available at: [http://www.ejcancer.com/article/S0959-8049\(14\)70131-5/abstract](http://www.ejcancer.com/article/S0959-8049(14)70131-5/abstract).
238. FDA approves belzutifan for cancers associated with von Hippel-Lindau disease. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-belzutifan-cancers-associated-von-hippel-lindau-disease>. Accessed December 20, 2021.
239. Srinivasan R, Donskov F, Iliopoulos O, et al. Phase 2 study of belzutifan (MK-6482), an oral hypoxia-inducible factor 2α (HIF-2α) inhibitor, for Von Hippel-Lindau (VHL) disease-associated clear cell renal cell carcinoma (ccRCC). Journal of Clinical Oncology 2021;39:4555-4555. Available at: https://doi.org/10.1200/JCO.2021.39.15_suppl.4555.
240. Jonasch E, Donskov F, Iliopoulos O, et al. Belzutifan for renal cell carcinoma in von hippel-lindau disease. N Engl J Med 2021;385:2036-2046. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34818478>.
241. Jonasch E, McCutcheon IE, Gombos DS, et al. Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-centre, phase 2 trial. Lancet Oncol 2018;19:1351-1359. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30236511>.