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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# Kidney Cancer

Version 2.2025 — September 6, 2024

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# NCCN Guidelines Version 2.2025

## Kidney Cancer

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**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](#).

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

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### Updates in Version 2.2025 of the NCCN Guidelines for Kidney Cancer from Version 1.2025 include:

#### KID-3

- T4, M0 pathway was added.
  - ▶ Primary Treatment
    - ◊ Resectable pathway: Adjuvant pembrolizumab was added as a category 2A recommendation for clear cell histology.
- Bottom pathway specified as M1.

#### KID-4

- Header revised: *Relapse or Stage IV or Relapsed Disease*

#### KID-D (1 of 3)

- Header revised: Principles of Systemic Therapy for *Relapse or Stage IV (M1 or Unresectable T4, M0) or Relapsed Disease* (Also for KID-D 3 of 3)

#### KID-D (2 of 3)

- Header revised: Principles of Systemic Therapy for *Relapse or Stage IV or Relapsed Disease*

#### KID-D (3 of 3)

- Footnote f added: For first-line only.

### Updates in Version 1.2025 of the NCCN Guidelines for Kidney Cancer from Version 4.2024 include:

#### KID-1

- Stage II and III moved to KID-2.
- Footnote a revised: Imaging with and without contrast is strongly preferred, such as a renal protocol *for abdomen*.
- Footnote d revised: Stereotactic body radiation therapy (SBRT) may be considered for ~~medically inoperable patients~~ *non-optimal surgical candidates* with stage I kidney cancer (category 2B) or with stage II/III kidney cancer (both category 3). See *Principles of Radiation Therapy (KID-B)*.

#### KID-2

- Clear cell histology, stage II and III pathways: Adjuvant pembrolizumab changed from a category 2A to a category 1 recommendation.
- Stage II, Clear cell histology: Adjuvant sunitinib was removed.

#### KID-4

- Footnote h added: *Principles of Radiation Therapy (KID-B)*.
- Footnote i revised: Best supportive care can include *palliative radiation therapy (RT) where SBRT is the preferred approach*, bisphosphonates, or receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors for bony metastases. An FDA-approved biosimilar is an appropriate substitute for denosumab.

#### KID-A

- General Principles of Management for Renal Cell Carcinoma
  - ▶ Bullet 6, sub-bullet 1 added: Thermal ablation is suitable for renal masses  $\leq 3$  cm.
  - ▶ Bullet 6, sub-bullet 4 revised: Ablative techniques may require *retreatment multiple treatments* to achieve the same local oncologic outcomes as conventional surgery.
  - ▶ Bullet 7 revised: SBRT is considered an ablative therapy and may be considered for ~~medically inoperable patients (not non-optimal surgical candidates)~~ with stage I (category 2B), II, or III (both category 3) kidney cancer.
  - ▶ Bullet 8, sub-bullet 1 revised: Small Renal masses  $< 3$  cm given the high rates of benign tumors and low metastatic potential of these masses.

#### KID-B

- New section added: *Principles of Radiation Therapy*

#### KID-C (1 of 5)

- Follow-up
  - ▶ Follow-up During Active Surveillance
    - ◊ Bullet 3, sub-bullet revised: Abdominal CT or MRI *both* with and without IV contrast (*unless otherwise contraindicated*) if no contraindication within 6 months of surveillance initiation, then CT, MRI, or ultrasound (US) at least annually
  - ▶ Follow-up After Ablative Techniques
    - ◊ Bullet 3, sub-bullet 1 revised: Abdominal CT or MRI *both* 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
- Footnote removed: CT is with IV contrast and MRI is with or without contrast. (Also for KID-C 2 through 4)



### Updates in Version 1.2025 of the NCCN Guidelines for Kidney Cancer from Version 4.2024 include:

#### KID-C (2 of 5)

- Stage I
  - ▶ Follow-up After a Partial or Radical Nephrectomy
    - ◊ Bullet 3, sub-bullet 1 revised: Baseline abdominal CT or MRI (preferred) *both with and without IV contrast (unless otherwise contraindicated)* within 3–12 months of surgery, then annually for up to 5 years or longer as clinically indicated
- Stage II
  - ▶ Follow-up After a Partial or Radical Nephrectomy
    - ◊ Bullet 3, sub-bullet 1 revised: Baseline abdominal CT or MRI (preferred) *both with and without IV contrast (unless otherwise contraindicated)*, every 6 months for 2 years, then annually for up to 5 years or longer as clinically indicated

#### KID-C (3 of 5)

- Follow-up for Stage III
  - ▶ Bullet 3, sub-bullet 1 revised: Baseline abdominal CT or MRI *both with and without IV contrast (unless otherwise contraindicated)* 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 for up to 5 years

#### KID-C (4 of 5)

- Follow-up for Relapsed or Stage IV and Surgically Unresectable Disease
  - ▶ Bullet 3, sub-bullet 1 revised: CT or MRI imaging *both with and without IV contrast (unless otherwise contraindicated)* to assess baseline pretreatment or prior to observation

#### KID-D (1 of 3)

- First-Line Therapy for Clear Cell Histology
  - ▶ Useful in Certain Circumstances
    - ◊ Favorable and Poor/intermediate risk: High-dose IL-2d was removed.
    - ◊ Poor/intermediate risk: Temsirolimus was removed.
  - ▶ Other Recommended Regimens, favorable risk: Ipilimumab + nivolumab was moved to Preferred Regimens.
- Footnote removed: Patients with excellent performance status and normal organ function. (Also for KID-D 2)
- Footnote removed: 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. (Also for KID-D 2 and KID-D 3 of 3)

#### KID-D (2 of 3)

- Subsequent Therapy for Clear Cell Histology
  - ▶ Useful in Certain Circumstances
    - ◊ IO Therapy Naïve and Prior IO Therapy: High-dose IL-2d was removed.
    - ◊ IO Therapy Naïve and Prior IO Therapy: Temsirolimus was removed

#### KID-D (3 of 3)

- Systemic Therapy for Non-Clear Cell Histology
  - ▶ Preferred Regimens
    - ◊ Lenvatinib + pembrolizumab was added as a category 2A recommendation.
  - ▶ Other Recommended Regimens
    - ◊ Cabozantinib + nivolumab was moved to Preferred Regimens.
  - ▶ Useful in Certain Circumstances
    - ◊ Erlotinib + bevacizumab + for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated RCC was moved to Other Recommended Regimens.
    - ◊ Bevacizumab was removed.
    - ◊ Erlotinib was removed.
    - ◊ Pazopanib was removed.
    - ◊ Temsirolimus was removed.



Updates in Version 1.2025 of the NCCN Guidelines for Kidney Cancer from Version 4.2024 include:

**HERED-RCC-A**

- Table 2: Features of Von Hippel-Lindau (VHL) Disease
  - ▶ Major Features
    - ◊ Bullet 2 revised: Clear cell RCC (ccRCC) diagnosed <40 years of age or multiple/bilateral ccRCC tumors diagnosed at any age

**HERED-RCC-B (1 of 2)**

- Table header, column 1 revised: *Syndrome Gene*
  - ▶ Row 1 revised: Abdominal MRI (preferred) or CT, *both exams obtained with and without IV contrast, every 2 y starting at age 30 y*
  - ▶ Row 2 revised: Abdominal MRI (preferred) or CT, *both exams obtained with and without IV contrast, every 3 y starting at age 20 y*
  - ▶ Row 3 revised: Abdominal MRI (preferred) or CT, *both exams obtained with and without IV contrast, every 3 y starting at age 8–10 y*
  - ▶ Row 4 revised: Abdominal MRI (preferred) or CT, *both exams obtained with and without IV contrast, every 1–2 y starting at age 30 y*
  - ▶ Row 5 revised: Abdominal MRI (preferred) or CT, *both exams obtained with and without IV contrast, every 2 years concurrently with PGL/PCC screening recommendations 4–6 y starting at age 12 y*
  - ▶ Row 6 revised: Abdominal MRI (preferred) or CT, *both exams obtained with and without IV contrast, every 1–3 3–5 y starting at age 12 y*
  - ▶ Row 7 revised: Abdominal MRI (preferred) or CT, *both exams obtained with and without IV contrast, to assess kidneys, pancreas, and adrenals every 2 y starting at age 15 y*
- Footnote a added: See NCCN Guidelines for Neuroendocrine and Adrenal Tumors for full screening recommendations.

**HERED-RCC-B (2 of 2)**

- Reference 8 revised: 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. Northrup H, Aronow ME, Bebin EM, et al. Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. *Pediatr Neurol* 2021;123:50–66.

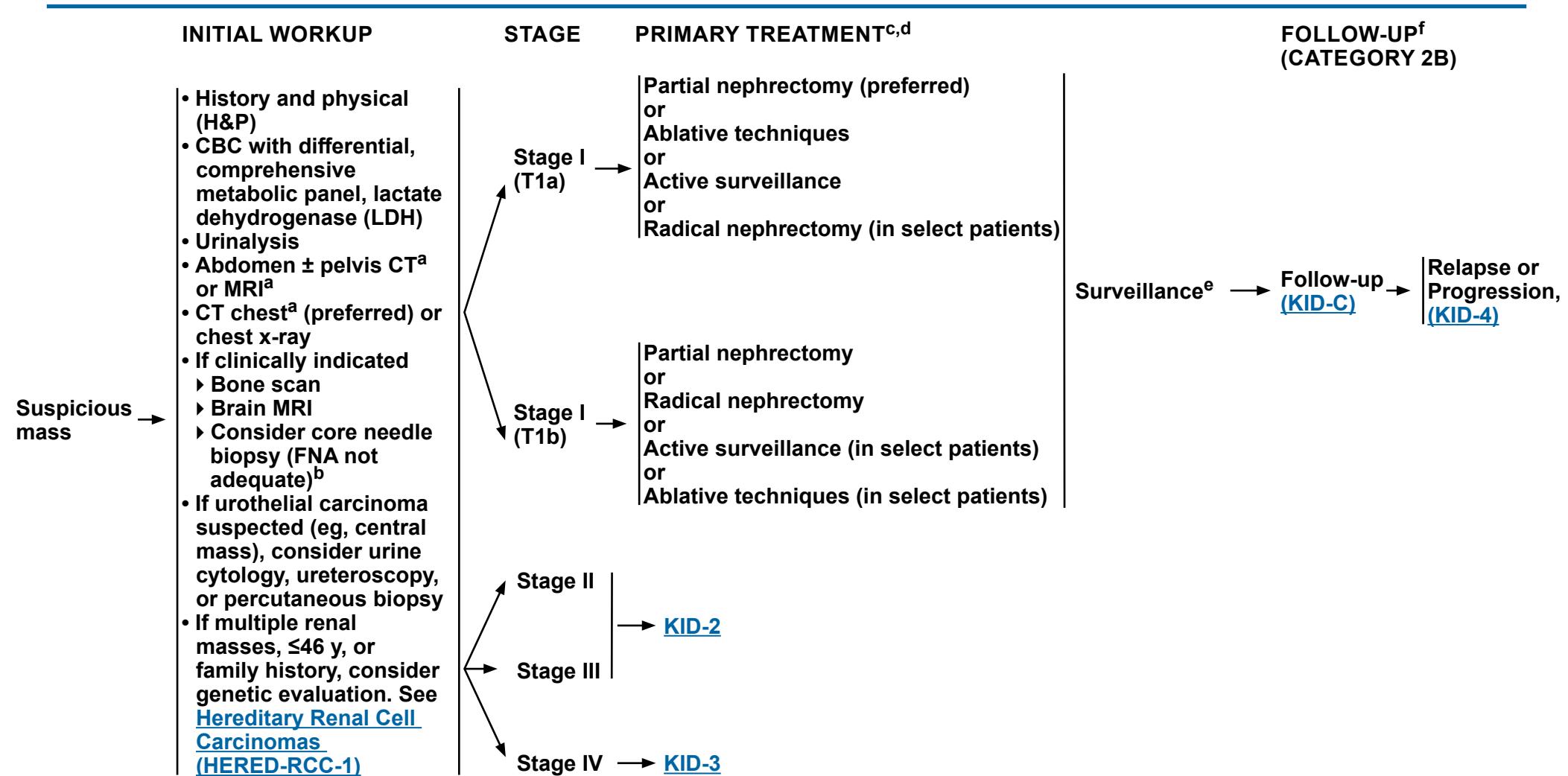
**HERED-RCC-D**

- HLRCC
  - ▶ Erlotinib + bevacizumab was changed from a Useful in Certain Circumstances to an Other Recommended Regimen recommendation.
  - ▶ Cabozantinib + nivolumab was added as a category 2A, Useful in Certain Circumstances recommendation.
- TSC
  - ▶ Everolimus was changed from a Useful in Certain Circumstances to a Preferred Regimen recommendation.
  - ▶ Sirolimus was added as a category 2A, Other Recommended Regimen recommendation.
- Footnote c added: NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
- Reference 3 added: Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. *N Engl J Med* 2008;358:140–151.



# NCCN Guidelines Version 2.2025

## Kidney Cancer



<sup>a</sup> Imaging with and without contrast is strongly preferred, such as a renal protocol for abdomen.

<sup>b</sup> 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.

<sup>c</sup> [General Principles of Management for Renal Cell Carcinoma \(KID-A\)](#).

<sup>d</sup> Stereotactic body radiation therapy (SBRT) may be considered for non-optimal surgical candidates with stage I kidney cancer (category 2B) or with stage II/III kidney cancer (both category 3). See [Principles of Radiation Therapy \(KID-B\)](#).

<sup>e</sup> [Follow-up \(KID-C\)](#).

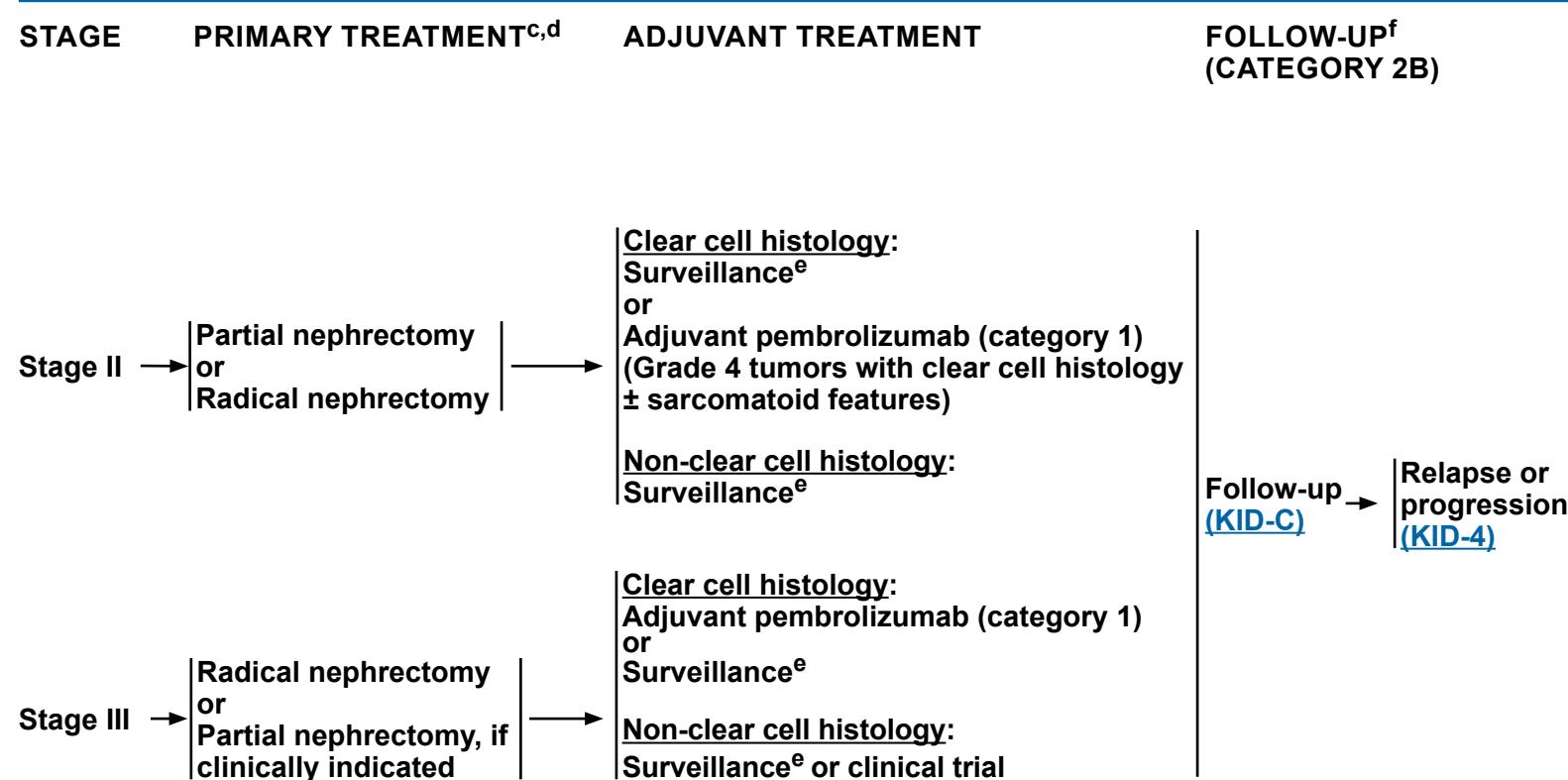
<sup>f</sup> No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

**Note:** All recommendations are category 2A unless otherwise indicated.



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## Kidney Cancer



<sup>c</sup> [General Principles of Management for Renal Cell Carcinoma \(KID-A\).](#)

<sup>d</sup> SBRT may be considered for non-optimal surgical candidates with stage I kidney cancer (category 2B) or with stage II/III kidney cancer (both category 3). See [Principles of Radiation Therapy \(KID-B\).](#)

<sup>e</sup> [Follow-up \(KID-C\).](#)

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

**Note:** All recommendations are category 2A unless otherwise indicated.



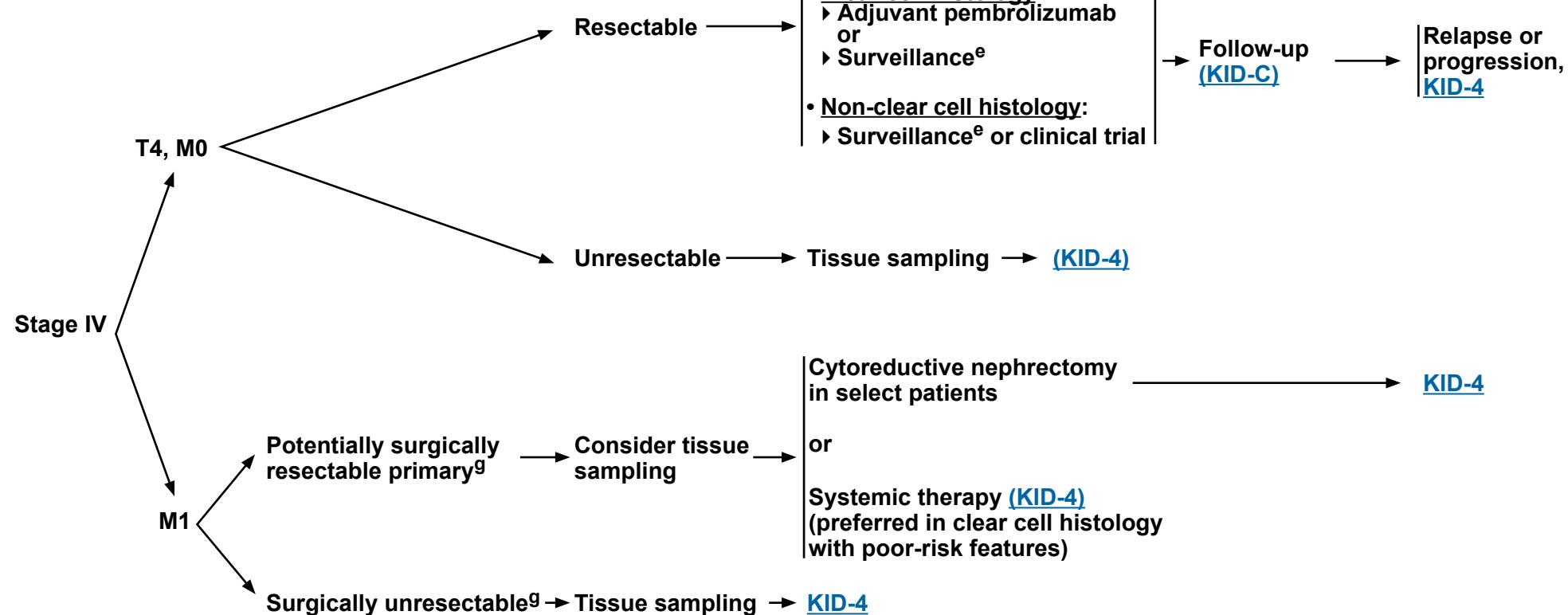
# NCCN Guidelines Version 2.2025

## Kidney Cancer

### STAGE

### PRIMARY TREATMENT<sup>c</sup>

### FOLLOW-UP<sup>f</sup> (CATEGORY 2B)



<sup>c</sup> [General Principles of Management for Renal Cell Carcinoma \(KID-A\)](#).

<sup>e</sup> [Follow-up \(KID-C\)](#).

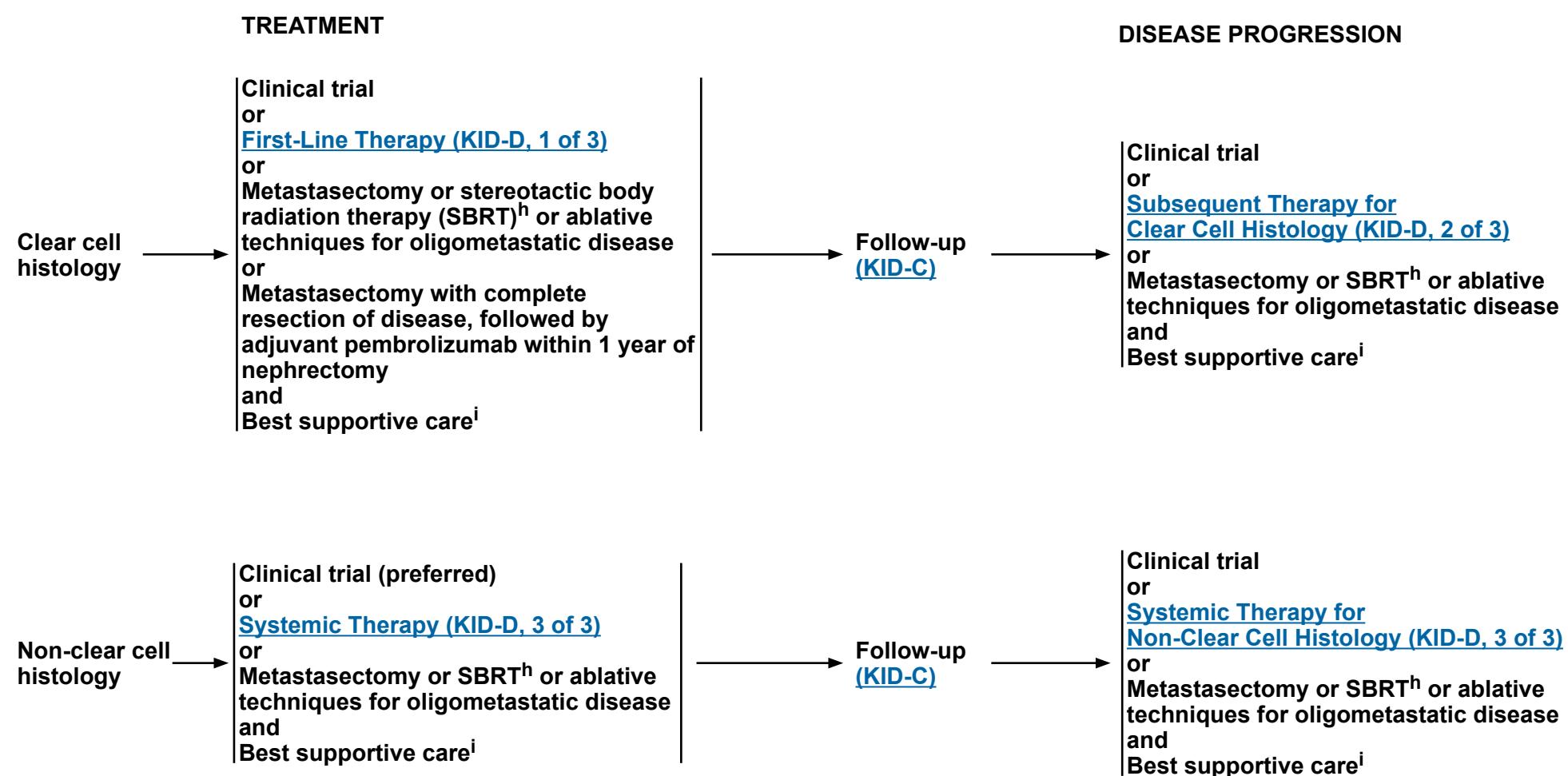
<sup>f</sup> No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

<sup>g</sup> Individualize treatment based on symptoms and extent of metastatic disease.

Note: All recommendations are category 2A unless otherwise indicated.



**STAGE IV OR RELAPSED DISEASE**



<sup>h</sup> [Principles of Radiation Therapy \(KID-B\)](#).

<sup>i</sup> Best supportive care can include radiation therapy (RT) where SBRT is the preferred approach, bisphosphonates, or receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors for bony metastases. An FDA-approved biosimilar is an appropriate substitute for denosumab.

**Note:** All recommendations are category 2A unless otherwise indicated.



### GENERAL PRINCIPLES OF MANAGEMENT FOR RENAL CELL CARCINOMA

- Nephron-sparing surgery (partial nephrectomy) is recommended in select patients, such as:
  - ▶ Patients with unilateral stage I–III tumors, where technically feasible
  - ▶ Patients with 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 suitable for renal masses  $\leq 3$  cm.
  - ▶ 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 retreatment to achieve the same local oncologic outcomes as conventional surgery.<sup>1,2</sup>
- SBRT is considered an ablative therapy and may be considered for non-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 clinical stage T1 renal lesions, for example:
  - ▶ It is an option for renal masses  $<2$  cm given the high rates of benign tumors and low metastatic potential of these masses.
  - ▶ Active surveillance of patients with T1a tumors ( $\leq 4$  cm) that have a predominantly cystic component is recommended.
  - ▶ It is an option for 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.

<sup>1</sup> Campbell S, Uzzo R, Allaf M, et al. Renal mass and localized renal cancer: AUA Guideline. J Urol 2017;198:520-529.

<sup>2</sup> 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: All recommendations are category 2A unless otherwise indicated.



## PRINCIPLES OF RADIATION THERAPY

### General Treatment Information:

- Consider radiation therapy (RT) in the following situations:

► **Modalities:** SBRT should be considered as the primary radiation modality in all situations unless precluded by anatomic site, proximity to organs at risk (OAR), or past treatments.

### Primary Disease:

- Definitive therapy<sup>1,2</sup>

► Definitive radiation using SBRT may be considered as a treatment option for non-optimal surgical candidates. Consider referral to a high-volume center with specialized expertise.

► **Patient selection:** SBRT can be considered for patients with T1 tumors (<7 cm in diameter). There are insufficient data to pursue SBRT in tumors >7 cm. Tumors abutting bowel should be considered NOT amenable to SBRT.

► **Dosing regimens:** SBRT should be delivered using over 1–5 fractions. Conventional fractionation is discouraged. Dose and fractionation options should attempt to keep the biologically effective dose (BED) to ≥80 Gy assuming an alpha/beta ratio of 10 due to association with improved local control. Established dosing regimens include:

- ◊ 26 Gy in 1 fraction
- ◊ 42–48 Gy in 3–4 fractions
- ◊ 40–50 Gy in 5 fractions

► For multi-fraction dosing, treatment can be delivered on consecutive or non-consecutive days.

► **Treatment technique:**

- ◊ For simulation and treatment planning 4D-CT and fusion with a renal protocol CT and/or renal MRI is strongly encouraged.
- ◊ Using an internal target volume (ITV) and/or motion management with respiratory gating is encouraged.
- ◊ Use of daily pretreatment imaging including MRI if available or cone-beam CT is recommended.
- ◊ OAR should be contoured to include a 3-mm planning OAR volume (PRV) and to account for motion on 4D-CT.<sup>a</sup>
- ◊ Use standard SBRT 5-fraction OAR constraints per the SWOG S1802 protocol (ClinicalTrials.gov identifier: NCT03678025).<sup>3,4</sup>

<sup>a</sup> For specific representative OAR dose constraints, see TROG 15.03 FASTRACK II Protocol: Siva S, et al. Lancet Oncol 2024;25:308-316.

Note: All recommendations are category 2A unless otherwise indicated.

References on [KID-B 4 of 5](#)

KID-B  
1 OF 5



## PRINCIPLES OF RADIATION THERAPY

### Distant Metastatic Disease:

- **Ablative treatment for intact extracranial metastases:**

- SBRT may offer more durable local control.<sup>5</sup> SBRT should be considered for patients with oligometastasis unless metastasectomy is planned or SBRT cannot be delivered due to anatomic site, proximity to OAR, or past treatments.<sup>5-10</sup> Strict adherence to normal tissue constraints is recommended. For multi-fraction dosing, treatment can be delivered on consecutive or non-consecutive days.

- **Spine SBRT regimens include but are not limited to:**

- 16–24 Gy in 1 fraction<sup>11</sup>
- 20–24 Gy in 2 fractions<sup>12</sup>
- 24–27 Gy in 3 fractions<sup>13</sup>
- 25–40 Gy in 5 fractions

- **SBRT regimens for other body sites include but are not limited to:**

- 16–24 Gy in 1 fraction<sup>11</sup>
- 48–60 Gy in 3 fractions<sup>5,14</sup>
- 35–60 Gy in 4–5 fractions<sup>5,15</sup>

- **Palliative treatment of symptomatic extracranial metastases:**

- A variety of treatment regimens are acceptable depending on location and/or clinical indication. Higher doses and/or hypofractionated regimens may be associated with more robust and durable palliation.<sup>11,16,17</sup> SBRT dosing and fractionation should be pursued when possible. Strict adherence to normal tissue constraints is recommended. For multi-fraction dosing, treatment can be delivered on consecutive or non-consecutive days.

- **Preferred regimens include:**

- 20–24 Gy in 2 fractions (spine only)<sup>12</sup>
- 24–27 Gy in 3 fractions<sup>18,19</sup>
- 32–48 Gy in 4 fractions<sup>20</sup>
- 30–50 Gy in 5 fractions
- 36 Gy in 6 fractions

- **Other potential regimens include:**

- 8 Gy in 1 fraction<sup>21</sup>
- 20 Gy in 5 fractions<sup>21</sup>
- 30 Gy in 10 fractions<sup>21</sup>

**Note:** All recommendations are category 2A unless otherwise indicated.

**References on KID-B 4 of 5**

**KID-B  
2 OF 5**

**PRINCIPLES OF RADIATION THERAPY****• Brain metastases:**

- ▶ **Stereotactic radiosurgery (SRS) and fractionated stereotactic RT (SRT)** are techniques for delivering a high dose of radiation to a specific target while delivering a minimal dose to surrounding tissues, generally in the brain and spine and in 1 to 5 sessions. Image-guided RT (IGRT) should be used to improve accuracy of radiotherapy delivery, where clinically appropriate.

**▶ SRS or SRT as primary treatment**

- ◊ Smaller tumors may be treated with maximal doses of 15–24 Gy in 1 fraction according to volume guidelines based on maximum tolerated dose results from the RTOG 90-05 dose escalation study (shown below).<sup>22</sup> Caution is recommended for lesions >3 cm, and single-fraction radiosurgery is not typically recommended for lesions >4 cm.
- Lesions with maximum diameter ≤20 mm receive up to 24 Gy
- Lesions with maximum diameter 21–30 mm receive up to 18 Gy
- Lesions with maximum diameter 31–40 mm receive up to 15 Gy
- ◊ Larger tumors, however, may be treated with fractionated SRT. Potential regimens include, but are not limited to:<sup>23,24</sup>
- 24–27 Gy in 3 fractions
- 25–35 Gy in 5 fractions

**▶ SRS/SRT as adjuvant treatment**

- ◊ Smaller cavities may be treated with single-fraction SRS maximal doses ranging from 12–20 Gy depending on cavity volume per the NCCTG N107C trial protocol.<sup>25</sup>
- Lesions <4.2 cc receive 20 Gy
- Lesions ≥4.2 cc to <8.0 cc receive 18 Gy
- Lesions ≥8.0 cc to <14.4 cc receive 17 Gy
- Lesions ≥14.4 cc to <20 cc receive 15 Gy
- Lesions ≥20 cc to <30 cc receive 14 Gy
- Lesions ≥30 cc to <5 cm receive 12 Gy
- ◊ In general, single-fraction adjuvant SRS is not recommended for cavities >5 cm.
- ◊ Larger cavities, however, may be treated with fractionated SRT. Potential regimens include, but are not limited to:
- 24–27 Gy in 3 fractions
- 25–35 Gy in 5 fractions

**▶ Palliative whole brain RT (WBRT)**

- ◊ Only consider for palliative purposes when SRS/SRT is not feasible in patients with good performance status for whom disease has progressed.
- ◊ The pros and cons of WBRT should be considered carefully in the context of individual patient preferences/goals of care.<sup>26</sup>
- ◊ WBRT can be considered if radiographic, clinical, or pathologic signs of leptomeningeal carcinomatosis are present (see LEPT-1 in the [NCCN Guidelines for Central Nervous System Cancers](#)).
- ◊ Common WBRT regimens include:
  - Standard doses include 30 Gy in 10 fractions and 20 Gy in 5 fractions. WBRT can be done with or without hippocampal avoidance (HA) + memantine. HA-WBRT (plus memantine) 30 Gy in 10 fractions is preferred for patients with a better prognosis (≥4 months) and no metastases within 5 mm of the hippocampi.<sup>27</sup>
  - For patients with poor predicted prognosis and with symptomatic brain metastases, standard WBRT of 20 Gy in 5 fractions is a reasonable option.<sup>28</sup> If WBRT is given, for patients with a better prognosis, consider memantine during and after WBRT for a total of 6 months.<sup>29</sup>

**▶ Adjuvant WBRT**

- ◊ Adjuvant WBRT after resection or SRS/SRT is not recommended for patients with kidney cancer.<sup>30</sup>
- Recent data from a randomized trial suggest that adjuvant WBRT is associated with worse cognitive decline when compared to adjuvant SRS/SRT alone.<sup>25</sup> Although local control appears superior with adjuvant WBRT, there were no differences in overall survival (OS).
- ◊ For dosing, see Palliative WBRT section above.
- ▶ Also see [NCCN Guidelines for Central Nervous System Cancers](#).

Note: All recommendations are category 2A unless otherwise indicated.

References on [KID-B 4 of 5](#)

KID-B

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## PRINCIPLES OF RADIATION THERAPY REFERENCES

- <sup>1</sup> Siva S, Louie AV, Kotecha R, et al. Stereotactic body radiotherapy for primary renal cell carcinoma: a systematic review and practice guideline from the International Society of Stereotactic Radiosurgery (ISRS). *Lancet Oncol* 2024;25:e18-e28.
- <sup>2</sup> Siva S, Bressel M, Sidhom M, et al. Stereotactic ablative body radiotherapy for primary kidney cancer (TROG 15.03 FASTRACK II): a non-randomised phase 2 trial. *Lancet Oncol* 2024;25:308-316.
- <sup>3</sup> Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: The report of AAPM Task Group 101. *Med Phys* 2010;37:4078-4101.
- <sup>4</sup> Chmura SJ, Winter KA, Woodward WA, et al. NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) for newly oligometastatic breast cancer (NCT02364557) [abstract]. *J Clin Oncol* 2022;40(Suppl):Abstract 1007.
- <sup>5</sup> Stinauer MA, Kavanagh BD, Schefter TE, et al. Stereotactic body radiation therapy for melanoma and renal cell carcinoma: impact of single fraction equivalent dose on local control. *Radiat Oncol* 2011;6:34.
- <sup>6</sup> Zaorsky NG, Lehrer EJ, Kothari G, et al. Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies. *Eur Urol* Oncol 2019;2:515-523.
- <sup>7</sup> Hannan R, Christensen M, Hammers H, et al. Phase II trial of stereotactic ablative radiation for oligoprogressive metastatic kidney cancer. *Eur Urol Oncol* 2022;5:216-224.
- <sup>8</sup> Tang C, Msaouel P, Hara K, et al. Definitive radiotherapy in lieu of systemic therapy for oligometastatic renal cell carcinoma: a single-arm, single-centre, feasibility, phase 2 trial. *Lancet Oncol* 2021;22:1732-1739.
- <sup>9</sup> Ali M, Mooi J, Lawrentschuk N, et al. The role of stereotactic ablative body radiotherapy in renal cell carcinoma. *Eur Urol* 2022;82:613-622.
- <sup>10</sup> Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomised, phase 2, open-label trial. *Lancet* 2019;393:2051-2058.
- <sup>11</sup> Gerszten PC, Burton SA, Quinn AE, et al. Radiosurgery for the treatment of spinal melanoma metastases. *Stereotact Funct Neurosurg* 2005;83:213-221.
- <sup>12</sup> Sahgal A, Roberge D, Schellenberg D, et al. The Canadian Association of Radiation Oncology scope of practice guidelines for lung, liver and spine stereotactic body radiotherapy. *Clin Oncol (R Coll Radiol)* 2012;24:629-639.
- <sup>13</sup> Wang XS, Rhines LD, Shiu AS, et al. Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1-2 trial. *Lancet Oncol* 2012;13:395-402.
- <sup>14</sup> Seung SK, Curti BD, Crittenden M, et al. Phase 1 study of stereotactic body radiotherapy and interleukin-2-tumor and immunological responses. *Sci Transl Med* 2012;4:137ra74.
- <sup>15</sup> Singh D, Chen Y, Hare MZ, et al. Local control rates with five-fraction stereotactic body radiotherapy for oligometastatic cancer to the lung. *J Thorac Dis* 2014;6:369-374.
- <sup>16</sup> Olivier KR, Schild SE, Morris CG, et al. A higher radiotherapy dose is associated with more durable palliation and longer survival in patients with metastatic melanoma. *Cancer* 2007;110:1791-1795.
- <sup>17</sup> Sahgal A, Myrehaug SD, Siva S, et al. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial. *Lancet Oncol* 2022;22:1023-1033.
- <sup>18</sup> Overgaard J, Gonzalez D, Hulshof MC, et al. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. *European Society for Hyperthermic Oncology*. *Lancet* 1995;345:540-543.
- <sup>19</sup> Overgaard J, von der Maase H, Overgaard M. A randomized study comparing two high-dose per fraction radiation schedules in recurrent or metastatic malignant melanoma. *Int J Radiat Oncol Biol Phys* 1985;11:1837-1839.
- <sup>20</sup> Sause WT, Cooper JS, Rush S, et al. Fraction size in external beam radiation therapy in the treatment of melanoma. *Int J Radiat Oncol Biol Phys* 1991;20:429-432.

Note: All recommendations are category 2A unless otherwise indicated.



## PRINCIPLES OF RADIATION THERAPY REFERENCES

- <sup>21</sup> Huguenin PU, Kieser S, Glanzmann C, et al. Radiotherapy for metastatic carcinomas of the kidney or melanomas: an analysis using palliative end points. *Int J Radiat Oncol Biol Phys* 1998;41:401-405.
- <sup>22</sup> Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys* 2000;47:291-298.
- <sup>23</sup> Minniti G, D'Angelillo RM, Scaringi C, et al. Fractionated stereotactic radiosurgery for patients with brain metastases. *J Neurooncol* 2014;117:295-301.
- <sup>24</sup> Rajakesari S, Arvold ND, Jimenez RB, et al. Local control after fractionated stereotactic radiation therapy for brain metastases. *J Neurooncol* 2014;120:339-346.
- <sup>25</sup> Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;18:1049-1060.
- <sup>26</sup> Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet* 2016;388:2004-2014.
- <sup>27</sup> Brown PD, Gondi V, Pugh S, et al. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: Phase III trial NRG Oncology CC001. *J Clin Oncol* 2020;38:1019-1029.
- <sup>28</sup> Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomized trial. *Lancet* 2004;363:1665-1672.
- <sup>29</sup> Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, doubleblind, placebo-controlled trial. *Neuro Oncol* 2013;15:1429-1437.
- <sup>30</sup> Hong AM, Fogarty GB, Dolven-Jacobsen K, et al. Adjuvant whole-brain radiation therapy compared with observation after local treatment of melanoma brain metastases: a multicenter, randomized phase III trial. *J Clin Oncol* 2019;37:3132-3141.

Note: All recommendations are category 2A unless otherwise indicated.



**FOLLOW-UP<sup>a</sup>**  
(category 2B)

**Stage I**

**Follow-up During Active Surveillance<sup>1-6</sup>**

- H&P annually
- Laboratory tests annually, as clinically indicated
- Abdominal imaging:
  - Abdominal CT or MRI both with and without IV contrast (unless otherwise contraindicated) 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<sup>1,7-10</sup>**

- H&P annually
- Laboratory tests annually, as clinically indicated
- Abdominal imaging:
  - Abdominal CT or MRI both 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

<sup>a</sup> 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-C, 5 of 5](#)). Further study is required to define optimal follow-up duration.

**Note:** All recommendations are category 2A unless otherwise indicated.



**FOLLOW-UP<sup>a</sup>**  
(category 2B)

**Stage I**

**Follow-up After a Partial or Radical Nephrectomy<sup>1</sup>**

- H&P annually
- Laboratory tests annually, as clinically indicated
- Abdominal imaging:
  - ▶ Baseline abdominal CT or MRI (preferred) both with and without IV contrast (unless otherwise contraindicated) 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 there are 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 there are positive margins or adverse pathologic features

**Stage II**

**Follow-up After a Partial or Radical Nephrectomy<sup>1</sup>**

- H&P annually
- Laboratory tests annually, as clinically indicated
- Abdominal imaging:
  - ▶ Baseline abdominal CT or MRI (preferred) both with and without IV contrast (unless otherwise contraindicated), 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 there are 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 there are positive margins or adverse pathologic features

<sup>a</sup> 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-C, 5 of 5](#)). Further study is required to define optimal follow-up duration.

**Note:** All recommendations are category 2A unless otherwise indicated.



**FOLLOW-UP<sup>a</sup>**  
(category 2B)

**Follow-up for Stage III<sup>1,11</sup>**

- H&P every 3–6 months for 3 years, then annually for 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 for up to 5 years, and as clinically indicated thereafter
- Abdominal imaging:
  - ▶ Baseline abdominal CT or MRI both with and without IV contrast (unless otherwise contraindicated) 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 for 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 for 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

<sup>a</sup> 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-C, 5 of 5](#)). Further study is required to define optimal follow-up duration.

**Note:** All recommendations are category 2A unless otherwise indicated.



**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<sup>b</sup>**

- 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 both with and without IV contrast (unless otherwise contraindicated) 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

<sup>b</sup> 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:** All recommendations are category 2A unless otherwise indicated.



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

**Long-Term Follow-Up (>5 years)<sup>2,12,13</sup>**

- 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.

<sup>1</sup> Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.

<sup>2</sup> 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.

<sup>3</sup> 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.

<sup>4</sup> 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.

<sup>5</sup> 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.

<sup>6</sup> 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.

<sup>7</sup> 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.

<sup>8</sup> Beksa 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.

<sup>9</sup> 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.

<sup>10</sup> 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.

<sup>11</sup> 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.

<sup>12</sup> 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.

<sup>13</sup> Dabestani S, Beisland C, Stewart GD, et al. Long-term outcomes of follow-up for initially localized clear cell renal cell carcinoma: RECUR database analysis. Eur Urol Focus 2019;5:857-866.

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 2.2025

## Kidney Cancer

### PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV (M1 OR UNRESECTABLE T4, M0) OR RELAPSED DISEASE

#### FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable <sup>a</sup>	<ul style="list-style-type: none"> <li>• Axitinib + pembrolizumab<sup>b</sup> (category 1)</li> <li>• Cabozantinib + nivolumab<sup>b</sup> (category 1)</li> <li>• Lenvatinib + pembrolizumab<sup>b</sup> (category 1)</li> <li>• Ipilimumab + nivolumab<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib + avelumab<sup>b</sup></li> <li>• Cabozantinib (category 2B)</li> <li>• Pazopanib</li> <li>• Sunitinib</li> </ul>	<ul style="list-style-type: none"> <li>• Active surveillance<sup>1,2,3</sup></li> <li>• Axitinib (category 2B)</li> </ul>
Poor/ intermediate <sup>a</sup>	<ul style="list-style-type: none"> <li>• Axitinib + pembrolizumab<sup>b</sup> (category 1)</li> <li>• Cabozantinib + nivolumab<sup>b</sup> (category 1)</li> <li>• Ipilimumab + nivolumab<sup>b</sup> (category 1)</li> <li>• Lenvatinib + pembrolizumab<sup>b</sup> (category 1)</li> <li>• Cabozantinib</li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib + avelumab<sup>b</sup></li> <li>• Pazopanib</li> <li>• Sunitinib</li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib (category 2B)</li> </ul>

#### Footnotes:

<sup>a</sup> [Risk Models to Direct Treatment \(IMDC criteria or MSKCC Prognostic Model\) \(KID-E\)](#).

<sup>b</sup> [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

#### References:

<sup>1</sup> 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.

<sup>2</sup> Harrison MR, Costello BA, Bhavsar NA, et al. Active surveillance of metastatic renal cell carcinoma: Results from a prospective observational study (MaRCC). Cancer 2021;127:2204-2212.

<sup>3</sup> Bex A. Increasing the evidence for surveillance of metastatic renal cancer. Cancer 2021;127:2184-2186.

**Note: All recommendations are category 2A unless otherwise indicated.**

**PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV OR RELAPSED DISEASE**

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	<ul style="list-style-type: none"> <li>• None</li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib + pembrolizumab<sup>b</sup></li> <li>• Cabozantinib</li> <li>• Cabozantinib + nivolumab<sup>b</sup></li> <li>• Everolimus + lenvatinib</li> <li>• Ipilimumab + nivolumab<sup>b</sup></li> <li>• Lenvatinib + pembrolizumab<sup>b</sup></li> <li>• Nivolumab<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib</li> <li>• Everolimus</li> <li>• Pazopanib</li> <li>• Sunitinib</li> <li>• Tivozanib<sup>d</sup></li> <li>• Belzutifan (category 2B)</li> <li>• Bevacizumab<sup>e</sup> (category 2B)</li> <li>• Axitinib + avelumab<sup>b</sup> (category 3)</li> </ul>
Prior IO Therapy	<ul style="list-style-type: none"> <li>• None</li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib</li> <li>• Belzutifan<sup>c</sup></li> <li>• Cabozantinib</li> <li>• Everolimus + lenvatinib</li> <li>• Tivozanib<sup>d</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib + pembrolizumab<sup>b</sup></li> <li>• Cabozantinib + nivolumab<sup>b</sup></li> <li>• Everolimus</li> <li>• Ipilimumab + nivolumab<sup>b</sup></li> <li>• Lenvatinib + pembrolizumab<sup>b</sup></li> <li>• Pazopanib</li> <li>• Sunitinib</li> <li>• Bevacizumab<sup>e</sup> (category 2B)</li> <li>• Axitinib + avelumab<sup>b</sup> (category 3)</li> </ul>

<sup>b</sup> [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).<sup>c</sup> This regimen is for patients who have received a programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).<sup>d</sup> For patients who received ≥2 prior systemic therapies.<sup>e</sup> An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

**Note:** All recommendations are category 2A unless otherwise indicated.



# NCCN Guidelines Version 2.2025

## Kidney Cancer

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### PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV (M1 OR UNRESECTABLE T4, M0)<sup>f</sup> OR RELAPSED DISEASE

#### SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY<sup>g</sup>

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> <li>• Clinical trial</li> <li>• Cabozantinib</li> <li>• Cabozantinib + nivolumab<sup>b</sup></li> <li>• Lenvatinib + pembrolizumab<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Erlotinib + bevacizumab<sup>e</sup> + for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated RCC (<a href="#">HERED-RCC-D</a>)</li> <li>• Everolimus + lenvatinib</li> <li>• Nivolumab<sup>b</sup></li> <li>• Pembrolizumab<sup>b</sup></li> <li>• Sunitinib</li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib</li> <li>• Everolimus + bevacizumab<sup>e</sup></li> <li>• Everolimus</li> <li>• Ipilimumab<sup>b</sup> + nivolumab<sup>b</sup> (category 2B)</li> </ul>

<sup>b</sup> [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

<sup>e</sup> An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

<sup>f</sup> For first-line only.

<sup>g</sup> 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: All recommendations are category 2A unless otherwise indicated.



## RISK MODELS TO DIRECT TREATMENT

### Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model<sup>1</sup>

#### 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<sup>2</sup>

#### 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: 2.0–7.0×10<sup>9</sup>/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

<sup>1</sup> 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.

<sup>2</sup> Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. *J Clin Oncol* 2009;27:5794-5799.

**Note:** All recommendations are category 2A unless otherwise indicated.



# NCCN Guidelines Version 2.2025

## Hereditary Renal Cell Carcinoma

### CRITERIA FOR FURTHER GENETIC RISK EVALUATION FOR HEREDITARY RCC SYNDROMES<sup>a</sup>

1. An individual with a close blood relative <sup>b</sup> with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene	→ <a href="#">GENE-1</a>
2. An individual with RCC with any of the following criteria:	→ Consider referral to cancer genetics professional and Refer to specific syndromes - See <a href="#">Hereditary RCC Syndromes Overview (HERED-RCC-2)</a> and <a href="#">NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic: Principles of Cancer Risk Assessment and Counseling (EVAL-A)</a> and <a href="#">Pedigree (EVAL-B)</a>
▶ Diagnosed at age ≤46 y <sup>c</sup>	
▶ Bilateral or multifocal tumors	
▶ ≥1 first- or second-degree relative <sup>b</sup> with RCC	
3. An individual whose tumors have the following histologic characteristics:	→ <a href="#">GENE-1</a>
▶ 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 ( <a href="#">Table 1</a> )	
▶ Succinate dehydrogenase (SDH)-deficient RCC histology <sup>d</sup>	
4. An unaffected individual <sup>e,f</sup> with any of the following criteria:	→ <a href="#">GENE-1</a>
▶ ≥2 first- or second-degree relatives <sup>b</sup> 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	

<sup>a</sup> 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.

<sup>b</sup> 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.

<sup>c</sup> Using age as a sole criterion for genetic risk evaluation is generally not a sensitive method.

<sup>d</sup> 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.)

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

<sup>f</sup> Unnecessary in translocational RCC or medullary RCC.

Note: All recommendations are category 2A unless otherwise indicated.



# NCCN Guidelines Version 2.2025

## Hereditary Renal Cell Carcinoma

### 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"> <li>Autosomal dominant</li> <li><a href="#">Table 2</a></li> </ul>	<ul style="list-style-type: none"> <li>Neurosurgery</li> <li>Ophthalmology</li> <li>Audiology</li> <li>Endocrinology</li> <li>Endocrine surgery</li> </ul>
Hereditary papillary renal carcinoma (HPRC)/ <i>MET</i> gene	Papillary	<ul style="list-style-type: none"> <li>Autosomal dominant</li> <li>Multifocal, bilateral renal cell tumors</li> </ul>	<ul style="list-style-type: none"> <li>Nephrology</li> </ul>
Birt-Hogg-Dubé syndrome (BHDS)/ <i>FLCN</i> gene <sup>1,2</sup>	Chromophobe, hybrid oncocytic tumors, clear cell, oncocytomas, angiomyolipomas, papillary RCC	<ul style="list-style-type: none"> <li>Autosomal dominant</li> <li>Cutaneous fibrofolliculoma or trichodiscoma, pulmonary cysts, and spontaneous pneumothorax</li> </ul>	<ul style="list-style-type: none"> <li>Pulmonology</li> <li>Dermatology</li> </ul>
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"> <li>Autosomal dominant</li> <li><a href="#">Table 1</a></li> </ul>	<ul style="list-style-type: none"> <li>Neurology</li> <li>Dermatology</li> </ul>
Hereditary leiomyomatosis and renal cell cancer (HLRCC)/ <i>FH</i> gene	HLRCC-associated RCC or FH-deficient RCC	<ul style="list-style-type: none"> <li>Autosomal dominant</li> <li>Leiomyomas of skin and uterus, unilateral, solitary, and aggressive renal cell tumors. PET-positive adrenal adenomas</li> </ul>	<ul style="list-style-type: none"> <li>Gynecology</li> <li>Dermatology</li> </ul>
<i>BAP1</i> tumor predisposition syndrome (TPDS)/ <i>BAP1</i> gene <sup>3,4</sup>	Clear cell	<ul style="list-style-type: none"> <li>Autosomal dominant</li> <li>Melanoma (uveal and cutaneous), kidney cancer, mesothelioma</li> </ul>	<ul style="list-style-type: none"> <li>Dermatology</li> <li>Ophthalmology</li> <li>Thoracic oncology</li> </ul>
Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome/ <i>SDHA/B/C/D</i> genes	SDH-deficient RCC	<ul style="list-style-type: none"> <li>Autosomal dominant</li> <li>Head and neck PGL and adrenal or extra-adrenal PCCs, gastrointestinal stromal tumors (GIST)</li> </ul>	<ul style="list-style-type: none"> <li>Endocrine</li> <li>Endocrine surgery</li> </ul>

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> 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.

<sup>4</sup> 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: All recommendations are category 2A unless otherwise indicated.

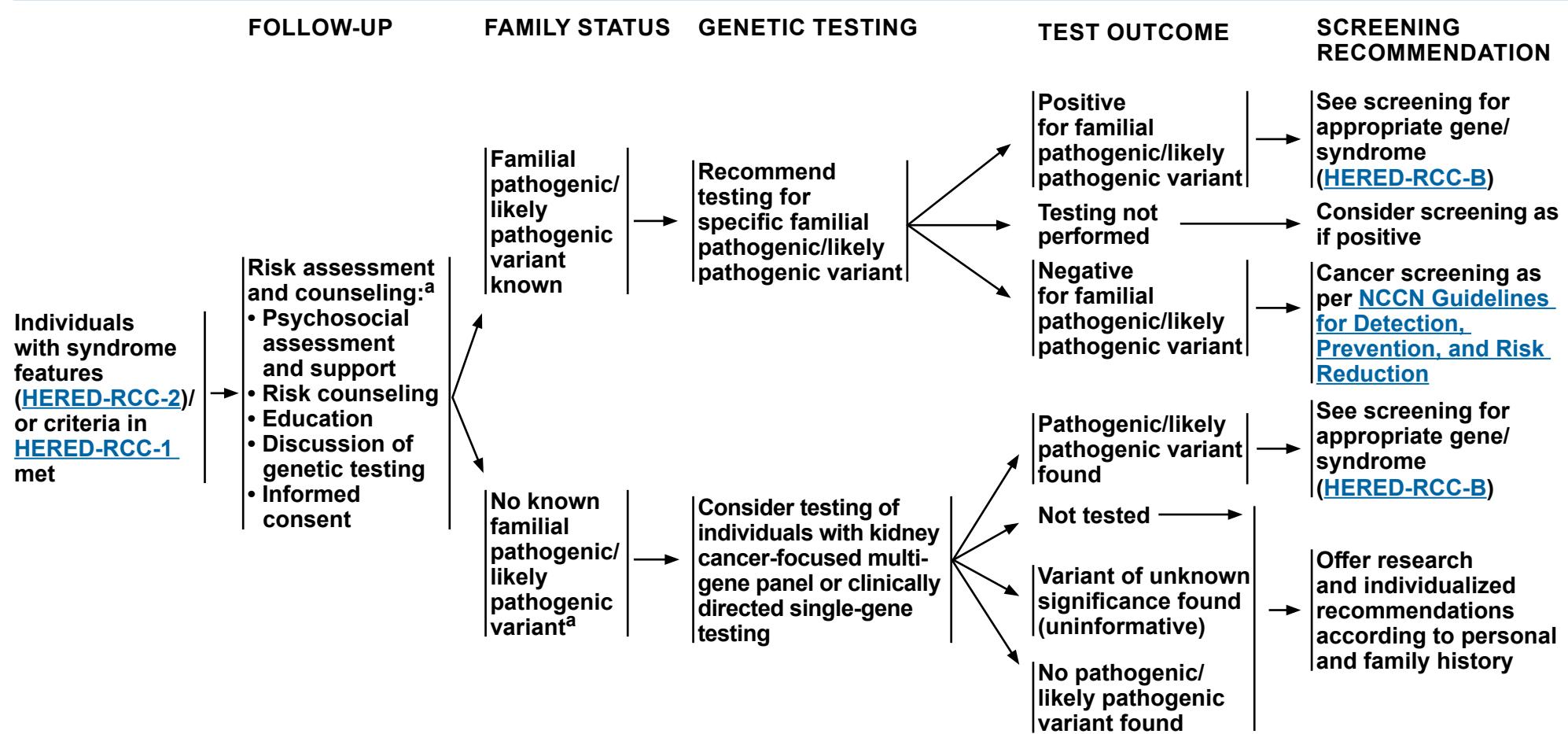
See [GENE-1](#)

**HERED-RCC-2**



# NCCN Guidelines Version 2.2025

## Hereditary Renal Cell Carcinoma



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

Note: All recommendations are category 2A unless otherwise indicated.



# NCCN Guidelines Version 2.2025

## Hereditary Renal Cell Carcinoma

Table 1: Features of Tuberous Sclerosis (TSC)

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

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

Major Features	Minor Features
<ul style="list-style-type: none"> <li>• Hemangioblastomas of the retina, spine, or brain</li> <li>• Clear cell RCC</li> <li>• Pheochromocytoma (PCCs)</li> <li>• PGL of abdomen, thorax, or neck</li> <li>• Retinal angiomas</li> </ul>	<ul style="list-style-type: none"> <li>• Endolymphatic sac tumors</li> <li>• Papillary cystadenomas of the epididymis or broad ligament</li> <li>• Pancreatic serous cystadenoma (<math>&gt; 1</math>)</li> <li>• Pancreatic neuroendocrine tumor (pNET) or multiple pancreatic cysts (<math>&gt; 1</math>)</li> </ul>

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

Note: All recommendations are category 2A unless otherwise indicated.



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## Hereditary Renal Cell Carcinoma

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### 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](#).

Syndrome	Screening Recommendations
BAP1-TPDS	• Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, every 2 y starting at age 30 y <sup>1</sup>
BHDS	• Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, every 3 y starting at age 20 y <sup>2</sup>
HLRCC	• Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, annually starting at age 8–10 y <sup>3</sup>
HPRC	• Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, every 1–2 y starting at age 30 y <sup>4,5</sup>
PGL/PCC <sup>a</sup>	• Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, every 2 years concurrently with PGL/PCC screening recommendations starting at age 12 y <sup>5,6,7</sup>
TSC	• Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, every 1–3 y starting at age 12 y <sup>8</sup>
VHL	• Abdominal MRI (preferred) or CT, both exams obtained with and without IV contrast, to assess kidneys, pancreas, and adrenals every 2 y starting at age 15 y <sup>5,9</sup>

<sup>a</sup> See [NCCN Guidelines for Neuroendocrine and Adrenal Tumors](#) for full screening recommendations.

Note: All recommendations are category 2A unless otherwise indicated.

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

**REFERENCES**

- <sup>1</sup> 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.
- <sup>2</sup> Menko F, van Steensel M, Giraud S, et al. Birt-Hogg-Dubé syndrome: Diagnosis and management. *Lancet Oncol* 2009;10:1199-1206.
- <sup>3</sup> 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.
- <sup>4</sup> 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.
- <sup>5</sup> 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.
- <sup>6</sup> Tufton N, Sahdev A, Akker SA. Radiological surveillance screening in asymptomatic succinate dehydrogenase mutation carriers. *J Endocr Soc* 2017;1:897-907.
- <sup>7</sup> 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.
- <sup>8</sup> Northrup H, Aronow ME, Bebin EM, et al. Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. *Pediatr Neurol* 2021;123:50-66.
- <sup>9</sup> 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:** All recommendations are category 2A unless otherwise indicated.

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# NCCN Guidelines Version 2.2025

## Hereditary Renal Cell Carcinoma

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### 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.<sup>1</sup>
- 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.<sup>2</sup>

#### 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.<sup>3</sup>

#### TSC

- Angiomyolipoma is a benign lesion associated with TSC and managed separately.<sup>4,5,6</sup>
- 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.<sup>7</sup>
- 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.”<sup>7</sup>
- 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.<sup>7,8</sup>
- 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.<sup>8</sup>
- 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: All recommendations are category 2A unless otherwise indicated.

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## KIDNEY-SPECIFIC SURGICAL RECOMMENDATIONS FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

### REFERENCES

- <sup>1</sup> 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.
- <sup>2</sup> 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.
- <sup>3</sup> 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.
- <sup>4</sup> 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.
- <sup>5</sup> Muller A, Rouviere O. Renal artery embolization—indications, technical approaches and outcomes *Nat Rev Nephrol* 2015;11:288-301.
- <sup>6</sup> Nelson CP, Sanda MG. Contemporary diagnosis and management of renal angiomyolipoma. *J Urol* 2002;168:1315-1325.
- <sup>7</sup> Shuch B, Singer EA, Bratslavsky G. The surgical approach to multifocal renal cancers. *Urol Clin North Am* 2012;39:133-148.
- <sup>8</sup> 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: All recommendations are category 2A unless otherwise indicated.

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# NCCN Guidelines Version 2.2025

## Hereditary Renal Cell Carcinoma

### KIDNEY-SPECIFIC SYSTEMIC THERAPY FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

Syndrome	Kidney-Specific Systemic Therapy
HLRCC	<b>Other Recommended Regimen</b> • Erlotinib + bevacizumab <sup>a,b,1</sup> <b>Useful in Certain Circumstances</b> • Cabozantinib + nivolumab <sup>c</sup>
TSC	<b>Preferred Regimen</b> • Everolimus <sup>d,2</sup> <b>Other Recommended Regimen</b> • Sirolimus <sup>3</sup>
VHL	<b>Preferred Regimen</b> • Belzutifan <sup>e,4</sup> <b>Useful in Certain Circumstances</b> • Pazopanib <sup>f,5</sup>

#### Footnotes:

<sup>a</sup> An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

<sup>b</sup> There are no specific FDA-approved therapies for HLRCC. Treatment with erlotinib plus bevacizumab demonstrated benefit in patients with metastatic RCC from HLRCC.

<sup>c</sup> [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

<sup>d</sup> Everolimus is an FDA-approved therapy for asymptomatic, growing angiomyolipoma measuring >3 cm in diameter.

<sup>e</sup> Belzutifan is FDA-approved for the treatment of VHL-associated-RCC, central nervous system (CNS) hemangioblastomas, or pNET, not requiring immediate surgery.

<sup>f</sup> Pazopanib was associated with a >50% objective response rate in renal lesions in a 31-patient phase II study.

#### References:

- <sup>1</sup> 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(Suppl):Abstract 5004.
- <sup>2</sup> 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.
- <sup>3</sup> Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med 2008;358:140-151.
- <sup>4</sup> 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.
- <sup>5</sup> 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:** All recommendations are category 2A unless otherwise indicated.



# NCCN Guidelines Version 2.2025

## Kidney Cancer

**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

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**Table 2. AJCC Prognostic Groups**

	<b>T</b>	<b>N</b>	<b>M</b>
<b>Stage I</b>	T1	N0	M0
<b>Stage II</b>	T2	N0	M0
<b>Stage III</b>	T1-T2	N1	M0
	T3	NX,N0-N1	M0
<b>Stage IV</b>	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**

BED	biologically effective dose	IMDC	International Metastatic Renal Cell Carcinoma Database Consortium	SBRT	stereotactic body radiation therapy
BHDS	Birt-Hogg-Dubé syndrome	IO	immuno-oncology	SDH	succinate dehydrogenase
CBC	complete blood count	ITV	internal target volume	SDHB	succinate dehydrogenase complex subunits B
CNS	central nervous system	LAM	lymphangioleiomyomatosis	SEGA	subependymal giant cell astrocytoma
ECOG	Eastern Cooperative Oncology Group	LDH	lactate dehydrogenase	SENs	subependymal nodules
		LLN	lower limit of normal	SRS	stereotactic radiosurgery
FH	fumarate hydratase	OAR	organ at risk	SRT	stereotactic radiation therapy
FNA	fine-needle aspiration	PCC	pheochromocytoma	TPDS	tumor predisposition syndrome
GIST	gastrointestinal stromal tumor	PD-1	programmed cell death protein 1	TSC	tuberous sclerosis complex
HA	hippocampal avoidance	PD-L1	programmed death ligand 1	ULN	upper limit of normal
H&P	history and physical	PGL	paraganglioma	VEGF-TKI	vascular endothelial growth factor tyrosine kinase inhibitor
HLRCC	hereditary leiomyomatosis and renal cell cancer	pNET	pancreatic neuroendocrine tumor	VHL	von Hippel-Lindau
HPRC	hereditary papillary renal carcinoma	PRV	planning organ at risk volume	WBRT	whole brain radiation therapy
IGRT	image-guided radiation therapy	RCC	renal cell carcinoma		
		RMC	renal medullary carcinoma		



# NCCN Guidelines Version 2.2025

## Kidney Cancer

### NCCN Categories of Evidence and Consensus

<b>Category 1</b>	Based upon high-level evidence ( $\geq 1$ randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ( $\geq 85\%$ support of the Panel) that the intervention is appropriate.
<b>Category 2A</b>	Based upon lower-level evidence, there is uniform NCCN consensus ( $\geq 85\%$ support of the Panel) that the intervention is appropriate.
<b>Category 2B</b>	Based upon lower-level evidence, there is NCCN consensus ( $\geq 50\%$ , but $< 85\%$ support of the Panel) that the intervention is appropriate.
<b>Category 3</b>	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

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

All recommendations are considered appropriate.



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### Discussion

This discussion corresponds to the NCCN Guidelines for Kidney Cancer. Last updated: May 30<sup>th</sup>, 2024

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### Overview

An estimated 81,610 Americans will be diagnosed with cancers of the kidney and renal pelvis and 14,390 will die of the disease in the United States in 2024.<sup>1</sup> These cancers comprise approximately 4.1% of all new cancers, with a median age at diagnosis of 65 years.<sup>2</sup> Approximately 85% of kidney tumors are renal cell carcinoma (RCC), and approximately 70% of these have a clear cell histology (clear cell RCC, ccRCC).<sup>3-5</sup> Other less common cell types include papillary, chromophobe, *TFE3*-rearranged, *TFEB*-altered (translocation) RCC, and collecting duct carcinoma.<sup>6</sup> *SMARCB1*-deficient medullary renal carcinoma is a rare and aggressive RCC variant that almost exclusively arises in patients who have sickle-cell trait or hemoglobin sickle cell disease, or rarely sickle cell disease.<sup>7</sup> The most recent pathologic classification system now has close to 20 types of RCC with several additional emerging entities.<sup>8</sup> 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 individuals to benign and malignant cysts/tumors.<sup>9-12</sup> Other hereditary types include fumarate hydratase (FH)-deficient and succinate dehydrogenase (SDH)-deficient RCC, associated with germline genetic alterations (also see *Heredity 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.<sup>2</sup> 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).<sup>13</sup> 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.<sup>14-23</sup> RCC primarily metastasizes to the lung, bone, liver, lymph nodes, adrenal gland, and brain.<sup>10,24,25</sup>

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer provide multidisciplinary recommendations for the clinical management of 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](http://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, RCC, renal 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;



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Guideline; Practice 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 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.<sup>26</sup> 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,<sup>27,28</sup> 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 ( $\leq 46$  years) may indicate an inheritable disorder,<sup>29</sup> 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.<sup>30,31,32</sup> 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.<sup>33,34</sup> All imaging studies should be performed with and without contrast, such as renal protocol.



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A central renal mass may suggest the presence of urothelial carcinoma; if so, urine cytology, ureteroscopy, or percutaneous mass biopsy 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.<sup>35</sup> MRI of the brain can be performed if clinical signs, presentation, and symptoms suggest brain metastases.

The recommended abdominal imaging studies provide high diagnostic accuracy. Therefore, a needle biopsy is not always necessary before surgery, especially in patients whose imaging studies are consistent with RCC. In selected individuals, needle biopsy may be considered to establish the diagnosis of RCC and to guide active surveillance strategies.

<sup>36</sup> Biopsy should be performed prior to or at the time of radiofrequency ablation, cryotherapy, or radiation therapy to confirm diagnosis and to guide surveillance strategies. 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.<sup>37</sup>

If patients present with multiple renal masses, are ≤46 years of age 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.<sup>38-45</sup>

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.<sup>46-51</sup> Radical nephrectomy can lead to an increased risk for chronic kidney disease<sup>52,53</sup> and is associated with increased risks of cardiovascular morbidity and mortality according to population-based studies.<sup>54</sup> When compared with radical nephrectomy, partial nephrectomy can achieve preserved renal function, decreased overall mortality, and reduced frequency of cardiovascular events.<sup>54-58</sup> 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.<sup>49,59-61</sup> Radical nephrectomy should not be employed when nephron sparing can be achieved. One study showed that among Medicare beneficiaries with early-stage kidney



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cancer, treatment with partial rather than radical nephrectomy was associated with improved survival.<sup>62</sup>

Studies with limited follow-up data show that the oncologic outcome for laparoscopic versus open nephron-sparing surgery appears to be similar.<sup>63,64</sup> 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.<sup>65</sup>

The goals of nephron-sparing surgery should be obtaining optimal locoregional tumor control while minimizing ischemia time to ideally less than 30 minutes.<sup>66</sup> However, in some patients with localized RCC, nephron-sparing surgery may not be suitable because of locally advanced 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.<sup>67</sup> 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.<sup>68</sup> 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.<sup>69</sup> 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.<sup>70</sup>

The NCCN Kidney Cancer Panel indicates regional lymph node dissection should be considered 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.<sup>71-73</sup> Adrenalectomy is not indicated when imaging shows a normal adrenal gland or if the tumor is not high risk, based on size and location.<sup>74</sup>

### Active Surveillance and Ablative Techniques

Active surveillance<sup>75,76</sup> is defined as the initial monitoring of tumors using abdominal imaging techniques with delayed intervention when indicated. The Panel recommends active surveillance as an option for certain patients with small renal masses (<3 cm), T1a tumors ( $\leq 4\text{cm}$ ), and competing comorbidities. Patients who are older and those with small renal masses and other comorbidities often have low RCC-specific mortality.<sup>77</sup> Active surveillance and ablative techniques such as cryotherapy, microwave ablation, or radiofrequency ablation are alternative strategies for selected patients, particularly for those who are older, those with competing health risks, and those with T1b masses not eligible for surgery. Stereotactic body radiation therapy (SBRT) may be considered for medically inoperable patients with stage I kidney cancer (category 2B) and with stage II/II 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.



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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 of developing progressive chronic kidney disease due to young age or medical risk factors (eg, hypertension, diabetes, nephrolithiasis). Both open and laparoscopic approaches to partial 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 (<3 cm), and, if required, treat for progression.<sup>75</sup>

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.<sup>78,79</sup> 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% confidence interval [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 (mean differences [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.<sup>80</sup> 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 RCC (T1a and in select patients with T1b tumors who are not surgical candidates).

### Management of Stage I (T1b) Disease

Partial nephrectomy for localized RCC has an oncologic outcome similar to that of radical surgery for T1b tumors.<sup>81,82</sup> Surgery by partial nephrectomy, whenever feasible, or by radical nephrectomy is the recommendation for clinical T1b tumors according to the NCCN Kidney Cancer Panel. Options for disease management in select patients are active surveillance or ablative techniques.

### Management of Stage II and III Disease

The curative therapy for patients with stages II and III disease remains radical nephrectomy.<sup>44</sup> 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.



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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 those 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 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 patients with locally advanced non-metastatic RCC with clear or non-clear histology, following nephrectomy.<sup>83</sup> 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 patients with high-risk ccRCC also did not demonstrate a DFS or OS benefit and reported high toxicity.<sup>84</sup> The ATLAS trial evaluating axitinib in the adjuvant setting also did not demonstrate a DFS benefit.<sup>85</sup>

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.<sup>86,87</sup> Median OS had not been reached in the sunitinib or placebo groups in either of these publications.<sup>86,87</sup> 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.<sup>88,89</sup>

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 cell death protein 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.<sup>90</sup> 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;  $P = .002$ ). The 30-month follow-up analysis was consistent with these data, demonstrating a clinical benefit of pembrolizumab in this setting.<sup>91</sup> Though median OS was not reached at 24 or 30 months, the percentage of patients who survived at 30 months was estimated to be



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95.7% in the pembrolizumab group versus 91.4% in the placebo group. Additionally, time to subsequent therapy or any-cause death was prolonged in those treated with pembrolizumab compared to placebo. Grade 3 or higher AEs occurred in 32.4% of pembrolizumab-treated patients versus 17.7% of those who received placebo.<sup>90,91</sup>

Based on the KEYNOTE-564 trial results, the Panel recommends considering 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 patients with stage 3 ccRCC, after a discussion with the patient about the potential benefits as well as the risks of adjuvant therapy. The Panel also recommends considering 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.<sup>92</sup>

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.<sup>93</sup> 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.<sup>94</sup> 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 I*

For follow-up during active surveillance, the Panel recommends an annual history and physical (H&P) 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 and without IV 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.<sup>95</sup> 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 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.



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### ***Follow-up After Ablative Therapy for Stage I***

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 and MRI with and without IV contrast (unless otherwise contraindicated), or contrast-enhanced US at 1 to 3 months, 6 months, and 12 months following ablation. Subsequent imaging is recommended annually. If the patient cannot receive IV contrast, MRI or contrast-enhanced US are preferred. If imaging results or clinical findings suggest residual disease or recurrence, then 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 H&P 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. 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.<sup>63,96,97</sup> 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 an H&P 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 III 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 patients with low-risk RCC, CT or MRI 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



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(UCLA) Integrated Staging System (UISS).<sup>98</sup> 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.<sup>98</sup>

### 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.<sup>99,100</sup>

The first prognostic factor model to be widely applied was from 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).<sup>99</sup> Prognostic factors for multivariable analysis included five variables: interval from diagnosis to treatment of <1 year; Karnofsky Performance Status (KPS) <80%; serum LDH >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 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.<sup>101</sup>

A prognostic model derived from a population of patients with metastatic RCC treated with VEGF-targeted therapy followed the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model.<sup>100</sup> 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 <80%, and time from the initial diagnosis to initiation of therapy of <1 year. Additional, independent, adverse prognostic factors validated in this model are absolute neutrophil count (ANC) greater than ULN and platelets greater than ULN.<sup>100</sup>

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%).<sup>100</sup> This model was validated in an independent dataset.<sup>102</sup>

#### 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 may be considered in select patients with a potentially surgically resectable primary tumor mass. A retrospective analysis conducted in the cytokine era indicated that



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patients most likely to benefit from cytoreductive nephrectomy before systemic therapy were those with lung-only metastases, good prognostic features, and good performance status.<sup>103</sup> Retrospective data from the IMDC suggested that cytoreductive nephrectomy continues to play a role in patients treated with VEGF-targeted agents.<sup>104</sup> 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.<sup>105</sup> 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.<sup>105,106</sup> 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).<sup>107</sup> 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.

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, SBRT or 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. Prospective phase II studies showed some patients may benefit from SBRT treatment for oligometastases, postponing time to systemic therapy.<sup>108,109</sup>

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. The Panel also recommends upfront systemic therapy for patients with large-volume distant metastases or large sarcomatoid tumors over initial cytoreductive nephrectomy.

Patients who have undergone a nephrectomy and years later develop an oligometastatic recurrence also have the option of metastasectomy, SBRT,<sup>110-112</sup> 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-



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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 based on the MSKCC Prognostic Model and the IMDC prognostic criteria.

### **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.

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 Categories of Preference.

### **First-Line Systemic Therapy Options for Patients with Clear Cell RCC**

#### ***Preferred Regimens***

##### ***Axitinib with Pembrolizumab (All Risk Groups)***

Axitinib is a selective, second-generation TKI of 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 tumor cells and antigen-presenting cells). In April 2019, the FDA approved axitinib in combination with pembrolizumab for first-line treatment of patients with advanced RCC.<sup>113,114</sup> 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. 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.<sup>115</sup> Subsequent analyses at 31- and 43-month median follow-ups showed agreement with these data (see *Table 1* for most recent efficacy data).<sup>116,117</sup> Median OS in the most recent follow-up was longer in the axitinib/pembrolizumab arm compared to the sunitinib arm.<sup>117</sup> Frequent AEs of grade 3 or higher in the axitinib/pembrolizumab arm included hypertension, diarrhea, and elevated alanine aminotransferase.<sup>116</sup> 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



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cabozantinib in combination with nivolumab for first-line treatment of patients with advanced RCC.<sup>118</sup> 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. 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.<sup>119</sup> In a subgroup analysis, the cabozantinib/nivolumab arm showed improved PFS, OS, and ORR in patients with advanced RCC with sarcomatoid features (an aggressive histologic subtype associated with poor prognosis) when compared to sunitinib.<sup>120</sup> Patients receiving combination treatment also reported delayed time to deterioration of patient-reported outcome scores compared to sunitinib.<sup>121</sup> Frequent AEs of grade 3 or 4 included hypertension, palmar-plantar erythrodysesthesia, and diarrhea.<sup>120</sup> In a median 55-month updated analysis, the cabozantinib/nivolumab combination continued to show clinically meaningful benefit over sunitinib, with longer OS and a duration of response (DOR) of 22 months versus 15.2 months (see *Table 1* for recent efficacy data).<sup>122</sup> 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- $\alpha$  (PDGFR- $\alpha$ ); 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.<sup>123</sup> 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. Patients received either lenvatinib/pembrolizumab, lenvatinib/everolimus, or sunitinib. Those receiving lenvatinib/pembrolizumab had significantly longer PFS and a higher ORR than those receiving sunitinib, which were maintained in follow-up analyses.<sup>124-126</sup> At median 49-month follow-up, OS was favorable for lenvatinib/pembrolizumab compared to sunitinib (see *Table 1* for most recent efficacy data).<sup>126</sup> In contrast, OS was not significantly different between the lenvatinib/everolimus and sunitinib groups.<sup>124</sup> The final analysis noted ~85% of patients treated with lenvatinib plus pembrolizumab had treatment-emergent AEs (grade 3 or higher), which included hypertension and diarrhea, versus ~75% of patients who received sunitinib, consistent with prior safety profile analyses.<sup>126</sup> 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.<sup>127</sup> 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.<sup>128</sup> The study's coprimary endpoints were ORR, OS, and PFS in patients with intermediate- and poor-risk RCC only; exploratory analyses of data in patients with favorable-risk RCC were reported separately (see *Other Recommended Regimens* for first-line, ccRCC below). In patients with intermediate-/poor-risk RCC, combination ipilimumab/nivolumab led to a



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higher ORR and CR rate versus sunitinib monotherapy. Follow-up at a median of 67.7 months showed a combined OS and ORR for all risk groups that favored ipilimumab plus nivolumab over sunitinib (see *Table 1* for updated efficacy data). For patients with intermediate-/poor-risk RCC, OS and PFS were significantly longer with ipilimumab/nivolumab versus sunitinib.<sup>129</sup> 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.<sup>128</sup> Based on these data, the Panel recommends first-line ipilimumab/nivolumab as a category 1, preferred treatment option for patients with poor- and intermediate-risk 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.<sup>130</sup> 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. The percentage of patients who experienced AEs of any grade or grade 3 or 4 was similar between cabozantinib and sunitinib. The most frequently reported AEs with cabozantinib included diarrhea, hypertension, fatigue, and palmar-plantar erythrodysesthesia.<sup>130</sup> Cabozantinib also increased quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) versus sunitinib (317 days vs. 180 days, respectfully, with no disease progression and no grade 3 or 4 AEs).<sup>131</sup>

Based on these results, the Panel recommends first-line cabozantinib as a category 2A, preferred treatment option for patients with poor- and intermediate-risk 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.<sup>132,133</sup> 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 primary<sup>132</sup> and 13-month interim<sup>133</sup> analyses. Extended follow-up showed that median OS was not reached for the axitinib/avelumab arm versus 37.8 months with sunitinib (see *Table 1* for efficacy data). Median PFS was significantly longer and ORR was higher with the combination versus sunitinib.<sup>134</sup> Incidence of AEs of any grade, or grade 3 or higher, was similar between treatment arms,<sup>132</sup> and no new safety signals were reported in the extended follow-up.<sup>134</sup> 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 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.<sup>135</sup>



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### *Cabozantinib (Favorable-Risk Group)*

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

### *Ipilimumab with Nivolumab (Favorable-Risk Group)*

The CheckMate 214 trial included patients with favorable-risk RCC treated with ipilimumab/nivolumab or sunitinib (see *Table 1* for efficacy data). In the median 67.7-month follow-up, there was no significant OS difference in the ipilimumab/nivolumab arm versus the sunitinib arm.<sup>129</sup> However, ORR and median PFS were lower in patients receiving ipilimumab/nivolumab than those receiving sunitinib. Notably, a higher proportion of patients achieved a CR with ipilimumab/nivolumab compared with those who received sunitinib, regardless of risk group.<sup>128,129,136</sup>

Based on these data, the Panel recommends first-line combination ipilimumab/nivolumab as a category 2A, other recommended regimen for the treatment of patients with ccRCC of favorable risk. 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- $\alpha$  and - $\beta$ , and stem cell factor receptor (c-KIT), interleukin-2 receptor-inducible T-cell kinase (ITK), lymphocyte-specific protein tyrosine kinase (LCK), and transmembrane glycoprotein receptor tyrosine kinase (c-FMS). 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,<sup>137</sup> but there was no difference in OS between the two groups.<sup>138</sup> Notable grade 3

toxicity was hepatotoxicity, indicated by elevated levels of alanine (30%) and aspartate (21%) transaminases.<sup>137</sup> 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).<sup>139,140</sup> 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- $\alpha$  and - $\beta$ ; 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).<sup>141–144</sup> 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- $\alpha$ .<sup>141</sup> 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- $\alpha$  in the first-line setting.<sup>145</sup> 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 surveillance through radiographic assessment at defined intervals until a decision was made to initiate systemic therapy.<sup>146</sup> Of the 48 patients included in the analysis, the median time of surveillance from registration



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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. In a prospective observational study of 504 patients with metastatic RCC, the median OS was not reached (95% CI, 122 months to not estimable [NE]) in patients who received active surveillance versus 30 months for those treated with systemic therapy.<sup>147,148</sup> 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.<sup>149</sup> 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.<sup>150</sup> 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.<sup>151-153</sup> For highly selected patients with ccRCC, first-line high-dose IL-2 has been designated as useful in certain circumstances (category 2B designation for patients at favorable risk for RCC and category 3 for patients at poor-/intermediate-risk for RCC).

### Tensirolimus (Poor-/Intermediate-Risk Groups)

Tensirolimus 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.<sup>154</sup> Patients received IFN- $\alpha$  alone, temsirolimus alone, or the combination of temsirolimus and IFN- $\alpha$ . Those who received temsirolimus alone showed improvement in OS and median PFS over those receiving IFN- $\alpha$  alone or combination therapy. AEs more frequent for those receiving temsirolimus compared to IFN- $\alpha$  were rash, stomatitis, hyperglycemia, hyperlipidemia, and peripheral edema.<sup>154</sup> Based on these data, the Panel has included first-line temsirolimus as a category 3, useful in certain circumstances option for patients with poor- and intermediate-risk ccRCC.

### Subsequent Systemic Therapy Options for Patients with Clear Cell RCC

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 registrational 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.



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### *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.<sup>155</sup> The final analysis of the METEOR trial showed a statistically significant increase in OS in the cabozantinib arm versus the everolimus arm.<sup>156,157</sup> Common grade 3 or 4 AEs that occurred more frequently with cabozantinib than with everolimus included hypertension, diarrhea, fatigue, hypomagnesaemia, and palmar-plantar erythrodysesthesia syndrome.<sup>155</sup> Additionally, a network meta-analysis comparing the relative effectiveness of subsequent treatment options for advanced and metastatic ccRCC found cabozantinib offered greater PFS, OS, and ORR benefit over everolimus, lenvatinib monotherapy, nivolumab, pazopanib, axitinib, sorafenib, temsirolimus, and tivozanib, but not over lenvatinib/everolimus combination. The odds of severe AEs were improved with cabozantinib over lenvatinib/everolimus and lenvatinib monotherapy.<sup>158</sup>

Based on these data, the Panel has included cabozantinib as a category 2A 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.<sup>159,160</sup> 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.<sup>161,162</sup> Diarrhea was the most common grade 3 or 4 AE for those receiving lenvatinib/everolimus.<sup>161</sup> A prospective study of 55 patients with metastatic ccRCC, heavily pretreated with prior ICIs and VEGFR-TKIs, showed a median PFS of 6.2 months and median OS of 12.2 months with lenvatinib/everolimus.<sup>163</sup> Based on the phase II trial data, the Panel considers lenvatinib/everolimus a category 2A 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 anti-angiogenic 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.<sup>164</sup> 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.<sup>165</sup> In the final analysis of Checkmate 025, long-term follow-up showed continued OS, PFS, and ORR benefit with nivolumab versus everolimus. The most prevalent grade 3 or 4 AEs with nivolumab were fatigue, anemia, and elevated levels of alanine and aspartate aminotransferases.<sup>166</sup> 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



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axitinib versus sorafenib.<sup>149</sup> Updated AXIS results showed that while OS did not significantly differ between the two groups, patients receiving axitinib had a continued improvement in PFS. The most prevalent AEs of grade 3 or higher for those treated with axitinib included hypertension, diarrhea, and fatigue.<sup>167</sup> 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,<sup>113,114</sup> 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 robust, 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. A retrospective study on 38 patients with ccRCC who had disease progression and previously received either ICI or VEGFR-TKI therapy were administered axitinib/pembrolizumab. Median PFS was 9.7 months (95% CI, 4.1–15.3) at a median follow-up of 17.1 months. The ORR was 25% (all partial responses [PRs]). Among 17 patients who had previously received ipilimumab/nivolumab and then second-line axitinib/pembrolizumab, the median PFS was 11.1 months and ORR was 31.4%. About 87% of patients in this study experienced AEs associated with the combination regimen, and hypertension, fatigue, and diarrhea were the most prevalent.<sup>168</sup> 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.

### *Cabozantinib with Nivolumab*

Apolo et al 2020<sup>169</sup> 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 abstract<sup>170</sup> 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–NE). Although there are no prospective or retrospective published data showing the benefit of cabozantinib/nivolumab in later lines of therapy in the treatment of advanced RCC, the Panel's decision was based on available data for combined ICI/TKI combinations of similar class such as lenvatinib/pembrolizumab and axitinib/pembrolizumab. 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. 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.<sup>171</sup> In a single-arm, phase II trial (TITAN-RCC), 32% of the 98 patients who had disease progression after second-line nivolumab had an objective response (OR) with ipilimumab/nivolumab. AEs of any grade occurred in 83% of patients, with grade 3 or 4 AEs occurring in 40% of patients.<sup>172</sup> In the randomized phase II FRACTION-RCC trial, patients whose disease progressed on or after IO therapy had an ORR of 17.4% on ipilimumab/nivolumab and median DOR of 16.4 months (see *Table 2*). Similarly to TITAN-RCC, AEs



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of any grade occurred in 78% of patients, with AEs of grade 3 or 4 occurring in 28%.<sup>173</sup> Two of the most common AEs of grade 3 or 4 reported in both trials were elevated lipase and diarrhea.<sup>172,173</sup> 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.<sup>174</sup> In a longer follow-up, the ORR for treatment-naïve, previously treated but ICI-naïve, and ICI-pretreated populations were consistent with previous observations (see *Table 2*). The median DOR was 24.2 months, 9 months, and 14.1 months, respectively. The longer follow-up data showed OS and PFS benefit for lenvatinib/pembrolizumab in all three treatment groups with the treatment-naïve population showing the highest benefit, followed by ICI-pretreated groups, and then the pretreated ICI-naïve group.<sup>175</sup> Hypertension, fatigue, and diarrhea were the most frequent treatment-related AEs and hypothyroidism was the most frequent immune-related AE.<sup>174</sup> 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 *Other Recommended Regimens* for first-line ccRCC, 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,<sup>137</sup> but OS was similar between the two groups.<sup>138</sup> 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%. AEs were mostly grade 1 or 2, and common grade 3 and 4 AEs included diarrhea and hypertension, similar to the phase III study.<sup>176</sup> 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.<sup>142,177</sup> 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.<sup>178-182</sup> Sunitinib is considered a category 2A, useful in certain 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 of VEGFR-1, -2, and 3; c-KIT; and PDGFR-β, for patients with relapsed or refractory advanced RCC who previously received two or more systemic



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therapies.<sup>183</sup> 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; median OS was similar between the two groups.<sup>184,185</sup> In the extended follow-up, a statistically meaningful, higher 12-month landmark, PFS-conditioned OS was observed in those treated with tivozanib versus sorafenib, suggesting that some patients may have an OS benefit with tivozanib.<sup>185</sup> Tivozanib also increased Q-TWiST as compared to sorafenib (15.04 months vs. 12.78 months, respectively).<sup>186</sup> Overall, incidence of AEs grade 3 or higher was lower in those treated with tivozanib compared to sorafenib. Common AEs grade 3 or higher were hypertension and asthenia.<sup>184,185</sup> Based on these data, the Panel considers tivozanib as a category 2A, other recommended subsequent therapy option for patients who have received at least 2 prior IO therapies and a useful in certain circumstances option for those who are IO therapy naïve but have received ≥2 prior systemic therapies.

### Axitinib with Avelumab

Extrapolating on the first-line JAVELIN Renal 101 data for patients with poor-/intermediate-risk (see *Other Recommended Regimens* for first-line, ccRCC), 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.<sup>187,188</sup> Common AEs included stomatitis, fatigue,

and rash, which generally were not severe. Pneumonitis of any grade was detected in <15% of patients treated with everolimus.<sup>187,188</sup> 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. In a phase II study investigating low- and high-dose bevacizumab versus placebo, bevacizumab extended time to progression of disease. Some patients receiving bevacizumab experienced hypertension or proteinuria, with no grade 4 or 5 AEs reported.<sup>189</sup> 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.<sup>190-194</sup> 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.<sup>195,196</sup> The Panel consensus did not support the inclusion of sorafenib as a subsequent therapy option for ccRCC.



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### Temsirolimus

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.<sup>197</sup> While a significant OS advantage was observed for sorafenib, PFS was similar between the two groups. Overall incidence of any AEs grade 3 or higher was similar between treatment arms, with anemia and hyperglycemia more common with temsirolimus than sorafenib.<sup>197</sup> The Panel considers temsirolimus a category 2B, useful in certain 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 $\alpha$  (HIF-2 $\alpha$ ) and blocks the heterodimerization of HIF-2 $\alpha$  with HIF-2 $\beta$ , 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. The most common AEs reported were anemia, fatigue, hypoxia, and dyspnea, among others.<sup>198</sup> Based on these results, belzutifan was considered well tolerated with a favorable safety profile as a single agent. Belzutifan was approved by the FDA for patients with advanced RCC who were previously treated with PD-1 or PD-L1 inhibitor and VEGF-TKI.<sup>199</sup> The open-label, randomized, phase III Litespark-005 trial compared belzutifan to everolimus in 746 patients with advanced ccRCC whose disease had progressed after first-line therapies.<sup>200</sup> At a median follow-up of 18.4 months, median PFS and ORR for belzutifan were significantly favorable compared to everolimus (see *Table 2*). The safety profile was similar to previous studies and incidence of grade 3–5 treatment-related AEs were similar between the two treatment arms.<sup>200</sup> Based on these data, the Panel included belzutifan as a category 2A, other recommended regimen for patients who had prior IO therapy, particularly those who

received PD-1/L1 and VEGF inhibitors. For patients who are IO therapy naïve, belzutifan is a category 2B, useful in certain circumstances subsequent therapy option for patients with ccRCC.

### Systemic Therapy for Patients with Non-Clear Cell RCC

Clinical trials of targeted agents have predominantly focused on patients with ccRCC due to the high prevalence of ccRCC.<sup>201</sup> 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.

#### *Non-Clear Cell RCC: 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.<sup>202</sup> See *Table 3* for efficacy data. Patients receiving cabozantinib had significantly longer PFS and a higher ORR than those receiving sunitinib. The incidence of AEs grade 3 or 4 was highest for cabozantinib (74%), and the most common grade 3 or 4 AEs for cabozantinib were hypertension, fatigue, and hand-foot syndrome. Based on these data, the Panel included cabozantinib as a category 2A, preferred option for patients with nccRCC.

#### *Non-Clear Cell RCC: Other Recommended Regimens*

##### *Sunitinib*

Two randomized phase II studies compared first-line sunitinib with first-line everolimus in patients with nccRCC. See *Table 3* for efficacy data. While



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data from the ASPEN trial<sup>203</sup> suggested that patients receiving sunitinib had significantly longer PFS than those receiving everolimus, data from the ESPN trial<sup>204</sup> suggested that both OS and PFS were similar between the two groups. Common AEs of grade 3 or 4 observed in both trials included hypertension, diarrhea, and fatigue. Other AEs of grade 3 or 4 in the ESPN trial that were of lower incidence in the ASPEN trial included neutropenia and anemia.<sup>203,204</sup>

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.<sup>205</sup> 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 and the phase II SWOG 1500 trial results,<sup>202</sup> the Panel decided sunitinib is a category 2A, other recommended option for patients with nccRCC.

### *Lenvatinib with Everolimus*

Extrapolating on data from the phase III lenvatinib/everolimus trial in patients with ccRCC<sup>161</sup> (see *Subsequent Systemic Therapy Options for Patients with ccRCC*), the Panel added the combination therapy as a category 2A, other recommended regimen for patients with nccRCC.

They also reviewed data<sup>206</sup> 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 DOR was NE. Eighteen patients (58.1%) had SD, and the clinical

benefit rate (CR + 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). AEs of any grade that occurred in >50% of patients included fatigue, diarrhea, nausea, vomiting, and decreased appetite.<sup>206</sup> 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.<sup>207</sup> 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. Fatigue, fever, rash, and hypothyroidism were the most common AEs observed. A separate retrospective analysis found modest responses with PD-1/PD-L1 inhibitors in 43 patients also with metastatic nccRCC.<sup>208</sup> 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.<sup>209</sup> 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). The most prevalent AEs of any grade were fatigue, diarrhea, and palmar-plantar erythrodysesthesia syndrome, and the most common grade 3 or 4 event was hypertension.<sup>209</sup> Study of patients with chromophobe RCC closed early due to the lack of efficacy. Based on these results, the Panel added nivolumab/cabozantinib as a category 2A, other recommended



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option for 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.<sup>210</sup> 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. Treatment-related AEs of any grade experienced by patients were most commonly pruritis, fatigue, hypothyroidism, and diarrhea.<sup>210</sup> Based on these data, the Panel added pembrolizumab as a category 2A, other recommended regimen for patients with nccRCC.

### Non-Clear Cell RCC: Useful in Certain Circumstances Regimens

#### Axitinib

A phase II trial of axitinib in 40 patients with recurrent or metastatic nccRCC that progressed after treatment with temsirolimus found a median PFS of 7.4 months, median OS of 12.1 months, and ORR of 37.5%. The most common AEs were hypertension, anorexia, cough, and plantar erythrodysthesia, which were mostly low grade.<sup>211</sup> 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 five patients with papillary RCC. The PFS reported for each of these patients was 25, 15, 11, 10, and 6 months. AEs of grades 1 and 2 were reported, which

included hypertension, proteinuria, and increased creatinine levels.<sup>212</sup> The Panel has included bevacizumab as a category 2A, useful in certain circumstances option for patients with nccRCC.

#### Bevacizumab with Erlotinib for Advanced Papillary RCC, Including Hereditary Leiomyomatosis and Renal Cell Carcinoma Associated RCC

Hereditary leiomyomatosis and renal cell carcinoma (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.<sup>213</sup> 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.<sup>214</sup> 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. The most frequent AEs of grade 1–2 were acneiform rash, diarrhea, proteinuria, and dry skin, and of grade 3 or higher were hypertension and proteinuria.<sup>214</sup> 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.<sup>215</sup> 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



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higher PFS and ORR than other histologies. Most AEs were grade 1 or 2, and AEs of grade 3 or 4 included hypertension, proteinuria, lymphopenia, hyperglycemia, and hypertriglyceridemia.<sup>215</sup> 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.<sup>216</sup> 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. AEs of grade 1 or 2 included diarrhea, fatigue, anorexia, and rash. About 24% of patients had an AE of grade 3 or higher.<sup>216</sup> 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.<sup>217</sup> In a phase II study of treatment-experienced patients with nccRCC,<sup>218</sup> median OS was 14 months, ORR was 10.2%, and median PFS was 5.2 months. About 47% of patients experienced AEs of grade 3 or higher, which included anemia and hyperglycemia.<sup>218</sup> According to data from the phase II RAPTOR trial,<sup>219</sup> median OS ranged from 24 to 28 months and median PFS ranged from 5 to 8 months, depending on type of papillary nccRCC; patients with type 1 nccRCC had better responses than those with type 2 histology. The most common AEs of any grade in >30% of patients were rash, cough, asthenia, mucosal inflammation, diarrhea, and decreased appetite.<sup>219</sup> 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 ≤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).<sup>220</sup> The most common AEs of any grade were rash, diarrhea/colitis, and hypothyroidism/thyroiditis. Reported AEs of grade 3 or 4 included diarrhea/colitis, rash, nephritis/renal dysfunction, adrenal insufficiency, hepatitis, and hypophysitis. The randomized phase II SUNNIFORECAST trial investigating nivolumab/ipilimumab in patients with untreated, advanced nccRCC is ongoing (NCT03075423). Based on this retrospective clinical evidence, the Panel added nivolumab/ipilimumab as category 2B option, useful in certain circumstances for advanced nccRCC.

### *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% and median PFS of 16.5 months. OS was not reached. Common AEs included hypertension, nausea/vomiting, hair color changes, diarrhea, mucositis, abdominal pain, and anorexia.<sup>221</sup> A retrospective analysis of an Italian multicenter cohort of 37 nccRCC patients found treatment with pazopanib to be effective and safe. Median PFS and OS were 15.9 months and 17.3 months, respectively.<sup>222</sup> Based on these data, the Panel considers pazopanib a category 2A, useful in certain circumstances option for patients with nccRCC. There is also an ongoing clinical trial evaluating the efficacy of second-line pazopanib in 38 patients



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with metastatic nccRCC, which has reported a median PFS of 7.5 months and OS of 18.9 months in patients receiving pazopanib.<sup>223</sup>

### Tensirolimus

A retrospective subset analysis of the global phase III ARCC trial demonstrated benefit of temsirolimus not only in ccRCC but also in nccRCC.<sup>154,224</sup> In patients with nccRCC (predominantly papillary RCC), the median OS and median PFS were 11.6 months and 7 months, respectively, with temsirolimus and 4.3 months and 1.8 months, respectively, with IFN- $\alpha$ . 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.<sup>225</sup> Temsirolimus is a useful in certain circumstances option for nccRCC; it has a category 1 designation for patients with poor-risk nccRCC and a category 2A designation for patients with favorable-/intermediate-risk nccRCC.

### *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.<sup>226,227</sup> Metastatic disease is seen at presentation in 67% to 95% of patients.<sup>226-228</sup> 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.<sup>229-232</sup> 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.<sup>233</sup> The results showed a response rate of 26% and an OS of 10.5 months.<sup>233</sup>

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.<sup>234,228,235</sup> 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 an H&P 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. 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.



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### 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.<sup>236</sup>

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.<sup>237-239</sup> 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.<sup>240,241</sup>

The role of bone-modifying agents such as bisphosphonates (eg, zoledronic acid) has been established in patients with various malignancies.<sup>242,243</sup> 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.<sup>244</sup> 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;  $P = .0007$ ).<sup>244</sup>

The Panel recommends a bisphosphonate or a RANK ligand inhibitor for selected patients with bony metastases and creatinine clearance  $\geq 30$  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),<sup>245</sup> 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 (FH-deficient), hereditary papillary renal carcinoma (HPRC), hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome (SDH-deficient), 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 syndrome. While published data informed the majority of these recommendations, the Panel also relied on the real-world experience and expertise of the hereditary



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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.<sup>11</sup>

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 or individuals with syndrome features should undergo genetic evaluation. For criteria to be met for further genetic risk evaluation for hereditary RCC syndromes and their histologies, inheritance patterns, and clinical manifestations, see *HERED-RCC-1* and *HERED-RCC-2* in the NCCN Guidelines for Kidney Cancer. If patients harbor a familial

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 abdominal 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,<sup>213</sup> those with less aggressive syndromes such as TSC may benefit from testing at longer intervals.<sup>246-249</sup>

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.<sup>213,246-250</sup> 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).<sup>246,251,252,253</sup> 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. This includes RCC diagnosis at ≤46 years of age (though not as sensitive when used as a single criterion),



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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,<sup>254,255</sup> while patients with HLRCC should undergo total radical nephrectomy.<sup>213</sup> 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.<sup>256</sup> 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).<sup>255,257</sup>

### **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.<sup>258,259</sup> 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. In a phase II study investigating erlotinib/bevacizumab treatment in patients with HLRCC or sporadic papillary RCC, erlotinib/bevacizumab treatment led to a 64% ORR and a median PFS of 21.1 months in patients with HLRCC-associated RCC.<sup>214</sup> 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.<sup>260</sup> Study-004, an open-label, phase II clinical trial, enrolled 61 patients with VHL-associated RCC; 97% had previously undergone a tumor reduction procedure.<sup>261</sup> 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. SD was identified in another 30 patients (49%). Median time to response was 8.2 months and



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median DOR was not reached.<sup>261</sup> The Panel considers belzutifan a category 2A, preferred option for patients with VHL-associated-RCC.

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.<sup>262</sup>

### Data Summary

The following tables summarize the key data supporting the inclusion of systemic therapy category 1 and 2A, preferred, and other recommended 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. For all tables, the most recent data are reported unless otherwise indicated.

Illustration update in progress



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**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)
<b>Combination Therapy</b>							
<b>JAVELIN Renal 101</b> Choueiri et al 2020 <sup>133</sup> Motzer et al 2019 <sup>132</sup> Haanen et al 2023 <sup>134</sup>	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+.	34	ORR: Overall population Axi/Ave: 59.3 (95% CI, 54.5–63.9) Sunitinib: 31.8 (95% CI, 27.4–36.3)	Overall population Axi/Ave: 13.9 (95% CI, 11.1–16.6) Sunitinib: 8.5 (95% CI, 6.7–9.8)  HR, 0.67 (95% CI, 0.568–0.785) <i>P</i> < .0001	Overall population Axi/Ave: NR (95% CI, 42.2–NE) Sunitinib: 37.8 (95% CI, 31.4–NE)  HR, 0.79 (95% CI, 0.643–0.969) <i>P</i> = .0116
	Sunitinib	444	In the extended follow-up, data for PD-L1+ patients were reported for PFS and OS.		CR (%): Overall population Axi/Ave: 4.8 Sunitinib: 3.2	PD-L1-positive Axi/Ave: 13.9 (95% CI, 11.0–17.8) Sunitinib: 8.2 (95% CI, 6.9–9.4)  HR, 0.58 (95% CI, 0.473–0.715) <i>P</i> < .0001	PD-L1-positive Axi/Ave: NR (95% CI, 40–NE) Sunitinib: 36.2 (95% CI, 30–NE)  HR, 0.81 (95% CI, 0.623–1.042) <i>P</i> = .0498
<b>KEYNOTE-426</b> Rini et al 2019 <sup>115</sup> Powles et al 2020 <sup>116</sup> Plimack et al 2023 <sup>117</sup>							
	Axitinib + pembrolizumab	432	Favorable-, intermediate-, or poor-risk, systemic therapy-naïve, advanced ccRCC; Karnofsky PS ≥70%	43	Axi/Pem: 60 (95% CI, 56–65) Sunitinib: 40 (95% CI, 35–44)	Axi/Pem: 16 (95% CI, 14–20) Sunitinib: 11 (95% CI, 8.9–13)  HR, 0.68 (95% CI, 0.58–0.80)	Axi/Pem: 46 Sunitinib: 40  HR, 0.73 (95% CI, 0.60–0.88)
	Sunitinib	429	Noted in the recent analysis: subset of patients in each arm received subsequent therapy after study treatment discontinuation				
<b>CheckMate 9ER</b> Choueiri et al 2021 <sup>119</sup> Motzer et al 2022 <sup>120</sup> Bourlon et al 2024 <sup>122</sup> (Conference Abstract)							
	Cabozantinib + nivolumab	323	Favorable-, intermediate-, or poor-risk, systemic therapy-naïve, advanced ccRCC; Karnofsky PS ≥70%	55.6	Cabo/Nivo: 55.7 (95% CI, 50.1–61.2) Sunitinib: 27.7 (95% CI, 23–32.9)	Cabo/Nivo: 16.4 Sunitinib: 8.4  HR, 0.58 (95% CI, 0.49–0.70)	Cabo/Nivo: 46.5 Sunitinib: 36  HR, 0.77 (95% CI, 0.63–0.95)
	Sunitinib	328					



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Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	Median PFS (months)	Median OS (months)
<b>CheckMate 214</b> Motzer et al 2018 <sup>128</sup> Motzer et al 2022 <sup>129</sup>	<b>Ipilimumab + nivolumab</b>	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	Ipi/Nivo: 39.3 Sunitinib: 32.4  <u>Intermediate-poor-risk</u> Ipi/Nivo: 42 (95% CI, 37–47) Sunitinib: 27 (95% CI, 23–31) $P < .0001$  <u>CR (%)</u> Ipi/Nivo: 11 Sunitinib: 2 $P < .001$	Ipi/Nivo: 12.3 Sunitinib: 12.3  <u>HR, 0.86</u> (95% CI, 0.73–1.01) $P = .0628$	Ipi/Nivo: 55.7 Sunitinib: 38.4  <u>HR, 0.72</u> (95% CI, 0.62–0.85) $P < .0001$
	Sunitinib	546			  <u>Favorable-risk</u> Ipi/Nivo: 30 (95% CI, 22–38) Sunitinib: 52 (95% CI, 43–61) $P < .001$  <u>CR (%)</u> Ipi/Nivo: 13 Sunitinib: 6	  <u>Intermediate-poor-risk</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) $P < .001$	  <u>Favorable-risk</u> Ipi/Nivo: 12.4 (95% CI, 9.7–18) Sunitinib: 28.9 (95% CI, 22.1–38.4)  <u>HR, 1.60</u> (95% CI, 1.13–2.26) $P < .01$
<b>CLEAR</b> Motzer et al 2021 <sup>124</sup> Choueiri et al 2023 <sup>125</sup> Motzer et al 2024 <sup>126</sup>  Note: For Len/Pem the most recent data are shown	<b>Lenvatinib + pembrolizumab</b>	355	Favorable-, intermediate-, or poor-risk, systemic therapy-naïve, advanced ccRCC; Karnofsky PS ≥70%	49	Len/Pem: 71.3 (95% CI, 66.6–76) Len/Ev: 54 Sunitinib: 36.7 (95% CI, 31.7–41.7)  <u>Len/Pem vs. Sunitinib</u> RR: 1.94 (95% CI, 1.67–2.26) $P < .0001$  <u>Len/Ev vs. Sunitinib</u> RR: 1.48 (95% CI, 1.26–1.74)  <u>CR</u> Len/Pem: 16 Len/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, 0.39 (95% CI, 0.32–0.49) $P < .0001$  <u>Len/Ev vs. Sunitinib</u> HR, 0.65 (95% CI, 0.53–0.80) $P < .001$	Len/Pem: 53.7 (95% CI, 48.7–NE) Len/Ev: NR Sunitinib: 54.3 (95% CI, 40.9–NE)
	<b>Lenvatinib + everolimus</b>	357				  <u>Len/Pem vs. Sunitinib</u> HR, 0.79 (95% CI, 0.63–0.99) $P = .0424$	  <u>Len/Ev vs. Sunitinib</u> HR, 1.15 (95% CI, 0.88–1.50) $P = .30$
	Sunitinib	357					



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Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	Median PFS (months)	Median OS (months)
<b>Monotherapy</b>							
<b>VEG105192</b> Sternberg et al 2013 <sup>138</sup> (OS data) Sternberg et al 2010 <sup>137</sup> (PFS and ORR data)	<b>Pazopanib</b>	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)	Pazopanib: 11.1 Placebo: 2.8  HR, 0.40 (95% CI, 0.27–0.60) <i>P</i> < .0001	Pazopanib: 23 Placebo: 24  HR, 1.01 (95% CI, 0.72–1.42) <i>P</i> value NR
	Placebo	145					
<b>COMPARZ</b> Motzer et al 2013 <sup>139</sup>  Note: In 2014, updated OS data were reported in a correspondence letter to the publishing journal. <sup>140</sup> Only the most recent OS data are shown.	<b>Pazopanib</b>	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					
<b>Phase III trial</b> Motzer et al 2007 <sup>141</sup>	<b>Sunitinib</b>	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					
<b>CABOSUN</b> Choueiri et al 2017 <sup>130</sup>	<b>Cabozantinib</b>	79	Intermediate- or poor-risk, systemic therapy-naïve, advanced or metastatic ccRCC, ECOG PS 0–2	21.4	Cabo: 33 (95% CI, 23–44) Sunitinib: 12 (95% CI, 5.4–21)	Cabo: 8.2 (95% CI, 6.2–8.8) Sunitinib: 5.6 (95% CI, 3.4–8.1)	Cabo: 30.3 (95% CI, 14.6–35) Sunitinib: 21.8 (95% CI, 16.3–27)  HR, 0.80 (95% CI, 0.50–1.26)
	Sunitinib	78					



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**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)
<b>Combination Therapy</b>							
<b>Phase I/II study</b> Apolo et al 2021 <sup>170</sup> (conference abstract)	Cabozantinib/nivolumab +/- ipilimumab	16	Favorable-, intermediate-, or poor-risk metastatic ccRCC; received at least one line of therapy; Karnofsky PS ≥70%	40.4	62.5	NR	38.6 (95% CI, 19.4–NE)
<b>FRACTION-RCC</b> Choueiri et al 2022 <sup>173</sup>  Note: Data for Track 2 patients who had prior IO therapy	Ipilimumab/nivolumab	46	Favorable-, intermediate-, or poor-risk advanced RCC; enrolled in 1 of 2 tracks; Karnofsky PS ≥70%. Patients in 2 tracks: Track 1 (IO therapy naïve, stratified according to previous TKI); Track 2 (prior IO), received 1 of 5 treatments containing nivolumab; patients in Track 1 who progressed were then enrolled in Track 2	33.8	17.4 (95% CI, 7.8–31.4)	3.7 (95% CI, 2–7.3)	23.8 (95% CI, 13.2–NE)
<b>Phase II study</b> Motzer et al 2016 <sup>162</sup> Motzer et al 2015 <sup>161</sup>	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: 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)  <u>Len/Ev vs. Ev</u> HR, 0.40 (95% CI, 0.24–0.68) <i>P</i> = .0005	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)  <u>Len/Ev vs. Ev</u> HR, 0.51 (95% CI, 0.30–0.88) <i>P</i> = .024	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)
	Everolimus	50					
	Lenvatinib	52					



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Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
KEYNOTE-146 Lee et al 2021 <sup>174</sup> Lee et al 2023 <sup>175</sup>	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	2+L, ICI-naïve: 52.9 2+L, ICI-TE: 62.5 TN: 77.3	2+L, ICI-naïve: 11.8 (95% CI, 5.5–18.6) 2+L, ICI-TE: 11.6 (95% CI, 7.6–14.1) TN: 22.1 (95% CI, 11.6–31.7)	2+L, ICI-naïve: 30.3 (95% CI, 28.7–NE) 2+L, ICI-TE: 32.1 (95% CI, 26.4–NE) TN: 55.8 (95% CI, 31.4–NE)
	Lenvatinib/pembrolizumab, ICI treatment-experienced (2+L ICI-TE)	104					
	Lenvatinib/pembrolizumab, treatment-naïve (TN)	22					
<b>Monotherapy</b>							
AXIS Motzer et al 2013 <sup>167</sup> Rini et al 2011 <sup>149</sup>	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 <sup>157</sup> Choueiri et al 2016 <sup>156</sup> Choueiri et al 2015 <sup>155</sup>	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 <sup>157</sup> ORR, PFS: 19 <sup>156</sup>	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	Cabo: 21.4 Ev: 17.1 HR, 0.70 (95% CI, 0.58–0.85) <i>P</i> = .0002
	Everolimus	328					
CheckMate 025 Motzer et al 2015 <sup>164</sup> Motzer et al 2020 <sup>166</sup>	Nivolumab	406	Favorable-, intermediate-, or poor-risk advanced or metastatic ccRCC; received 1–2 prior antiangiogenic therapies (except mTOR inhibitors); Karnofsky PS ≥70%	72	Nivo: 22.9 (95% CI, 18.9–27.3) Ev: 4.1 (95% CI, 2.4–6.5) OR, 6.86 (95% CI, 4–11.7) <i>P</i> < .0001	Nivo: 4.2 (95% CI, 3.7–5.4) Ev: 4.5 (95% CI, 3.7–5.5) HR, 0.84 (95% CI, 0.72–0.99) <i>P</i> = .0331	Nivo: 25.8 (95% CI, 22.2–29.8) Ev: 19.7 (95% CI, 17.6–22.1) HR, 0.73 (95% CI, 0.62–0.85) <i>P</i> < .0001
	Everolimus	397					



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Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
<b>VEG105192</b> Sternberg et al 2013 <sup>138</sup> (OS data)  Sternberg et al 2010 <sup>137</sup> (PFS and ORR data)	<b>Pazopanib</b>	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 (95% CI, 19.3–28.3) Placebo: 19 (95% CI, 14.2–26.3)  HR, 0.82 (95% CI, 0.57–1.16) <i>P</i> value NR
	Placebo	145					
<b>TIVO-3</b> Rini et al 2020 <sup>184</sup> Beckermann et al 2024 <sup>185</sup> (extended follow-up for PFS and OS)	<b>Tivozanib</b>	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  Extended follow-up: HR, 0.624 (95% CI, 0.49–0.79) <i>P</i> < .0001	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  12-mo landmark PFS-conditioned OS: Tivo: 48.3 Sor: 32.8  HR, 0.45 (95% CI, 0.22–0.91) <i>P</i> = .0221
	Sorafenib	175					
<b>LITESPARK-005</b> Albiges et al 2023 <sup>200</sup> (conference abstract)  Note: at median follow-up of 25.7 mo, PFS, ORR, and OS were similar, so data from 1 follow-up are shown	Belzutifan	374	Unresectable, locally advanced, or metastatic ccRCC; 1–3 prior therapies, progressed PD-1 or PD-L1 inhibitor and VEGF-targeted TKI; Karnofsky PS ≥70%	18.4	Bel: 21.9 (95% CI, 17.8–26.5) Ev: 3.5 (95% CI, 1.9–5.9)	Bel: 5.6 Ev: 5.6  HR, 0.75 (95% CI, 0.63–0.90) <i>P</i> < .001	Bel: 21 Ev: 17.2  HR, 0.87 (0.71–1.07) <i>P</i> = .096
	Everolimus	372					



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**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)
<b>Combination Therapy</b>							
<b>Phase II trial</b> Hutson et al 2021 <sup>206</sup>	<b>Lenvatinib/everolimus</b>	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)
<b>Phase II, cohort study</b> Lee et al 2022 <sup>209</sup>	<b>Nivolumab/cabozantinib</b>	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)
<b>Monotherapy</b>							
<b>Phase II SWOG 1500 trial</b> Pal et al 2021 <sup>202</sup>  Note: The trial also included savoritinib and crizotinib groups; assignment was halted after a futility analysis.	<b>Cabozantinib</b>	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  $P = .010$	Cabo: 9.0 (95% CI, 6–12) Sun: 5.6 (95% CI, 3–7)  HR, 0.60 (95% CI, 0.37–0.97) $P = .019$	Cabo: 20.0 Sun: 16.4  HR, 0.84 (95% CI, 0.47–1.51) Not significant
	<b>Sunitinib</b>	44					
<b>Retrospective study</b> Koshkin et al 2018 <sup>207</sup>	<b>Nivolumab</b>	35	Metastatic nccRCC	9	PR: 20 SD: 29	3.5	NR
<b>Phase II KEYNOTE-427 (cohort B)</b> McDermott et al 2021 <sup>210</sup>	<b>Pembrolizumab</b>	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)



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Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
<b>Phase II ASPEN trial</b> Armstrong et al 2016 <sup>203</sup>	Sunitinib	51	Favorable-, intermediate-, or poor-risk, systemic therapy-naïve metastatic nccRCC (papillary, chromophobe, or unclassified); Karnofsky PS ≥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					
<b>Phase II ESPN trial</b> Tannir et al 2016 <sup>204</sup>	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					



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### References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024;74:12-49. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38230766>.
2. SEER cancer stat facts: Kidney and renal pelvis cancer. Bethesda, MD: National Cancer Institute; Available at: <https://seer.cancer.gov/statfacts/html/kidrp.html>. Accessed February 7, 2024.
3. 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>.
4. 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>.
5. 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>.
6. Moch H, Amin MB, Berney DM, et al. The 2022 World Health Organization classification of tumours of the urinary system and male genital organs-part a: renal, penile, and testicular tumours. Eur Urol 2022;82:458-468. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35853783>.
7. 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>.
8. Trpkov K, Hes O, Williamson SR, et al. New developments in existing WHO entities and evolving molecular concepts: The Genitourinary Pathology Society (GUPS) update on renal neoplasia. Mod Pathol 2021;34:1392-1424. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33664427>.
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/](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



# NCCN Guidelines Version 2.2025

## Kidney Cancer

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* 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. Freedman-Cass DA, Fischer T, Alpert AB, et al. The value and process of inclusion: Using sensitive, respectful, and inclusive language and images in NCCN content. *J Natl Compr Canc Netw* 2023;21:434-441. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37156485>.

27. 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>.

28. 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>.

29. Shuch B, Vourgant 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>.

30. 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>.

31. 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>.



# NCCN Guidelines Version 2.2025

## Kidney Cancer

32. Sheth S, Scataglie 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>.
33. 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>.
34. 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>.
35. 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>.
36. 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>.
37. 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>.
38. 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>.
39. 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>.
40. 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>.
41. 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>.
42. 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>.
43. 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>.
44. 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>.
45. 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>.
46. 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>.
47. 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*



# NCCN Guidelines Version 2.2025

## Kidney Cancer

2000;75:1236-1242. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/11126830>.

48. 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>.

49. 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>.

50. 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:  
<http://www.ncbi.nlm.nih.gov/pubmed/19195042>.

51. 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>.

52. 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>.

53. 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>.

54. 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>.

55. 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>.

56. 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>.

57. 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>.

58. 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>.

59. 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>.

60. 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>.

61. 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>.

62. 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>.

63. Gill IS, Kavoussi LR, Lane BR, et al. Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumors. *J*



National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 2.2025

## Kidney Cancer

Urol 2007;178:41-46. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17574056>.

64. 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>.

65. 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>.

66. 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>.

67. 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>.

68. 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>.

69. 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>.

70. 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>.

71. 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>.

72. 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>.

73. 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;181:2009-2017. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19286216>.

74. 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>.

75. 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>.

76. 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>.

77. 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>.

78. 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>.

79. Pierorazio PM, Johnson MH, Patel HD, et al. Management of renal masses and localized renal cancer: Systematic review and meta-analysis.



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Cancer  
Network®

# NCCN Guidelines Version 2.2025

## Kidney Cancer

J Urol 2016;196:989-999. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27157369>.

80. 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>.

81. 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>.

82. 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>.

83. 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>.

84. Motzer RJ, Haas NB, Donskov F, et al. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. J Clin Oncol 2017;35:3916-3923. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/28902533>.

85. 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>.

86. 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>.

87. 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>.

88. 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>.

89. 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>.

90. 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>.

91. Powles T, Tomczak P, Park SH, et al. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2022;23:1133-1144. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/36055304>.

92. 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>.

93. 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>.

94. Dabestani S, Beisland C, Stewart GD, et al. Long-term outcomes of follow-up for initially localised clear cell renal cell carcinoma: RECUR



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# NCCN Guidelines Version 2.2025

## Kidney Cancer

database analysis. Eur Urol Focus 2019;5:857-866. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29525381>.

95. 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>.

96. 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>.

97. 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>.

98. Lam JS, Shvarts O, Leppert JT, et al. Postoperative surveillance protocol for patients with localized and locally advanced renal cell 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>.

99. 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>.

100. 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>.

101. 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>.

102. 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>.

103. 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>.

104. 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>.

105. 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>.

106. 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>.

107. 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>.

108. Hannan R, Christensen M, Hammers H, et al. Phase II trial of stereotactic ablative radiation for oligoprogressive metastatic kidney cancer. Eur Urol Oncol 2022;5:216-224. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34986993>.

109. Tang C, Msaoel P, Hara K, et al. Definitive radiotherapy in lieu of systemic therapy for oligometastatic renal cell carcinoma: a single-arm,



National  
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Network®

# NCCN Guidelines Version 2.2025

## Kidney Cancer

single-centre, feasibility, phase 2 trial. Lancet Oncol 2021;22:1732-1739.  
Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34717797>.

110. 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>.

111. 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>.

112. 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>.

113. 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.

114. Pembrolizumab injection, prescribing information. 2024. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/125514s1601bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125514s1601bl.pdf). Accessed April 17, 2024.

115. 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>.

116. 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>.

117. Plimack ER, Powles T, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib as first-line treatment of advanced renal cell carcinoma: 43-month follow-up of the phase 3 KEYNOTE-426 study. Eur Urol 2023;84:449-454. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37500340>.

118. 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 November 6, 2023.

119. 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>.

120. Motzer RJ, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial. Lancet Oncol 2022;23:888-898. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35688173>.

121. Celli 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>.

122. Bourlon MT, Escudier B, Burotto M, et al. Nivolumab plus cabozantinib (N+C) vs sunitinib (S) for previously untreated advanced renal cell carcinoma (aRCC): Results from 55-month follow-up of the CheckMate 9ER trial. J Clin Oncol 2024;42:362-362. Available at: [https://doi.org/10.1200/JCO.2024.42.4\\_suppl.362](https://doi.org/10.1200/JCO.2024.42.4_suppl.362).

123. FDA approves lenvatinib plus pembrolizumab for advanced renal cell carcinoma. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenvatinib-plus-pembrolizumab-advanced-renal-cell-carcinoma>. Accessed November 6, 2023.



# NCCN Guidelines Version 2.2025

## Kidney Cancer

124. 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>.
125. Choueiri TK, Eto M, Motzer R, et al. Lenvatinib plus pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma (CLEAR): extended follow-up from the phase 3, randomised, open-label study. *Lancet Oncol* 2023;24:228-238. Available at: <https://pubmed.ncbi.nlm.nih.gov/36858721/>.
126. Motzer RJ, Porta C, Eto M, et al. Lenvatinib plus pembrolizumab versus sunitinib in first-line treatment of advanced renal cell carcinoma: Final prespecified overall survival analysis of clear, a phase III study. *J Clin Oncol* 2024;42:1222-1228. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38227898>.
127. 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.
128. 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>.
129. Motzer RJ, McDermott DF, Escudier B, et al. Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma. *Cancer* 2022;128:2085-2097. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35383908>.
130. 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>.
131. Chen RC, Choueiri TK, Feuilly M, et al. Quality-adjusted survival with first-line cabozantinib or sunitinib for advanced renal cell carcinoma in the CABOSUN randomized clinical trial (Alliance). *Cancer* 2020;126:5311-5318. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33022096>.
132. 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>.
133. 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>.
134. Haanen J, Larkin J, Choueiri TK, et al. Extended follow-up from JAVELIN Renal 101: subgroup analysis of avelumab plus axitinib versus sunitinib by the International Metastatic Renal Cell Carcinoma Database Consortium risk group in patients with advanced renal cell carcinoma. *ESMO Open* 2023;8:101210. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37104931>.
135. 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>.
136. 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>.
137. 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>.



# NCCN Guidelines Version 2.2025

## Kidney Cancer

138. 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>.
139. 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>.
140. 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>.
141. 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>.
142. 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>.
143. 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>.
144. 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>.
145. 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>.
146. 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>.
147. Harrison MR, Costello BA, Bhavsar NA, et al. Active surveillance of metastatic renal cell carcinoma: Results from a prospective observational study (MaRCC). *Cancer* 2021;127:2204-2212. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33765337>.
148. Bex A. Increasing the evidence for surveillance of metastatic renal cancer. *Cancer* 2021;127:2184-2186. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33765328>.
149. 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>.
150. 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>.
151. 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>.
152. 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>.
153. 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 2.2025

## Kidney Cancer

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

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

154. 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>.

155. 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>.

156. 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>.

157. 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>.

158. Obeng-Kusi M, Kreutzfeldt JJ, Estrada-Mendizabal RJ, et al. Network meta-analysis of second line and beyond treatment options in metastatic clear cell renal cell carcinoma. Urol Oncol 2024;42:32 e31-32 e38. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38216444>.

159. Lenvatinib capsules, for oral use prescribing information. 2023.

Available at:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2023/206947s0281bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/206947s0281bl.pdf). Accessed March 7, 2024.

160. 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 November 6, 2023.

161. 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>.

162. 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>.

163. Wiele AJ, Bathala TK, Hahn AW, et al. Lenvatinib with or without everolimus in patients with metastatic renal cell carcinoma after immune checkpoint inhibitors and vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies. Oncologist 2021;26:476-482. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33792094>.

164. 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>.

165. 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>.

166. Motzer RJ, Escudier B, George S, et al. Nivolumab versus everolimus in patients with advanced renal cell carcinoma: Updated results with long-term follow-up of the randomized, open-label, phase 3 CheckMate 025 trial. Cancer 2020;126:4156-4167. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32673417>.

167. 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>.



# NCCN Guidelines Version 2.2025

## Kidney Cancer

168. Dizman N, Austin M, Considine B, et al. Outcomes with combination pembrolizumab and axitinib in second and further line treatment of metastatic renal cell carcinoma. *Clin Genitourin Cancer* 2023;21:221-229. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36681606>.
169. 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>.
170. Apolo AB, Girardi DdM, Niglio SA, et al. Final results from a phase I trial and expansion cohorts of cabozantinib and nivolumab (CaboNivo) alone or with ipilimumab (CaboNivoppi) for metastatic genitourinary tumors. *Journal of Clinical Oncology* 2021;39:3-3. Available at: [https://doi.org/10.1200/JCO.2021.39.6\\_suppl.3](https://doi.org/10.1200/JCO.2021.39.6_suppl.3).
171. 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>.
172. Grimm MO, Esteban E, Barthelemy P, et al. Tailored immunotherapy approach with nivolumab with or without nivolumab plus ipilimumab as immunotherapeutic boost in patients with metastatic renal cell carcinoma (TITAN-RCC): a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2023;24:1252-1265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37844597>.
173. Choueiri TK, Kluger H, George S, et al. FRACTION-RCC: nivolumab plus ipilimumab for advanced renal cell carcinoma after progression on immuno-oncology therapy. *J Immunother Cancer* 2022;10. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36328377>.
174. Lee CH, Shah AY, Rasco D, et al. Lenvatinib plus pembrolizumab in patients with either treatment-naïve 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>.
175. Lee C-H, Yogesh Shah A, Rao A, et al. Final database lock results of the phase 2 cohort of lenvatinib + pembrolizumab for progressive disease after a PD-1/PD-L1-containing therapy in metastatic clear cell renal cell carcinoma. *Oncologist* 2023;28:S3-S4. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10445556/>.
176. 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>.
177. 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>.
178. 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>.
179. 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>.
180. 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>.
181. 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>.
182. 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>.



# NCCN Guidelines Version 2.2025

## Kidney Cancer

183. 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 November 6, 2023.
184. 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>.
185. Beckermann KE, Asnis-Alibozek AG, Atkins MB, et al. Long-term survival in patients with relapsed/refractory advanced renal cell carcinoma treated with tivozanib: Analysis of the Phase III TIVO-3 trial. Oncologist 2024;29:254-262. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38262444>.
186. 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;19:468 e461-468 e465. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33980467>.
187. 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>.
188. 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>.
189. 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>.
190. 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 2005;92:1855-1861. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15870716>.
191. 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>.
192. 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>.
193. 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>.
194. 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>.
195. 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>.
196. 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>.



# NCCN Guidelines Version 2.2025

## Kidney Cancer

197. 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>.
198. Jonasch E, Bauer TM, Papadopoulos KP, et al. Phase I LITESPARK-001 study of belzutifan for advanced solid tumors: Extended 41-month follow-up in the clear cell renal cell carcinoma cohort. *Eur J Cancer* 2023;196:113434. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38008031>.
199. FDA approves belzutifan for advanced renal cell carcinoma. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-belzutifan-advanced-renal-cell-carcinoma>. Accessed December 19, 2023.
200. Albiges L, Rini B, Peltola K, et al. LBA88 Belzutifan versus everolimus in participants (pts) with previously treated advanced clear cell renal cell carcinoma (ccRCC): Randomized open-label phase III LITESPARK-005 study. *Ann Oncol* 2023;34:S1329-S1330. Available at: [https://www.annalsofoncology.org/article/S0923-7534\(23\)04234-5/fulltext](https://www.annalsofoncology.org/article/S0923-7534(23)04234-5/fulltext).
201. 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>.
202. 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>.
203. 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>.
204. 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>.
205. 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>.
206. Hutson TE, Michaelson MD, Kuzel TM, et al. A single-arm, multicenter, phase 2 study of lenvatinib plus everolimus in patients with advanced non-clear cell renal cell carcinoma. *Eur Urol* 2021;80:162-170. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33867192>.
207. 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>.
208. 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>.
209. 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;40:2333-2341. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35298296>.
210. 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>.
211. 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*



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# NCCN Guidelines Version 2.2025

## Kidney Cancer

2018;16:e997-e1002. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/29903415>.

212. 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](http://ascopubs.org/doi/abs/10.1200/jco.2011.29.15_suppl.e15158).

213. 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>.

214. 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. J Clin Oncol 2020;38:5004-5004. Available at:  
[https://doi.org/10.1200/JCO.2020.38.15\\_suppl.5004](https://doi.org/10.1200/JCO.2020.38.15_suppl.5004).

215. 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>.

216. 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>.

217. 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](http://ascopubs.org/doi/abs/10.1200/jco.2012.30.5_suppl.402).

218. 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>.

219. 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>.

220. 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 Immunother Cancer 2022;10. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/35210307>.

221. 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>.

222. 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>.

223. Costello BA, Ho TH, Perez Burbano G, et al. Phase II efficacy trial of pazopanib in nonclear cell metastatic renal cell cancer (mRCC): PINCR. J Clin Oncol 2020;38:696-696. Available at:  
[https://doi.org/10.1200/JCO.2020.38.6\\_suppl.696](https://doi.org/10.1200/JCO.2020.38.6_suppl.696).

224. 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>.

225. 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>.

226. 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>.



# NCCN Guidelines Version 2.2025

## Kidney Cancer

227. 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>.
228. 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>.
229. 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>.
230. 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>.
231. 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>.
232. 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>.
233. 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>.
234. 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>.
235. Roubaud G, Gross-Goupil 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>.
236. 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>.
237. 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>.
238. 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>.
239. 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>.
240. 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>.
241. 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>.



# NCCN Guidelines Version 2.2025

## Kidney Cancer

242. 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>.
243. 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>.
244. 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>.
245. 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>.
246. 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>.
247. 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>.
248. 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>.
249. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35709961>.
250. 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>.
251. 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>.
252. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29413689>.
253. 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>.
254. 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>.
255. 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>.
256. 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*



National  
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## NCCN Guidelines Version 2.2025 Kidney Cancer

2014;38:1588-1602. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25025441>.

257. 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>.

258. Everolimus tablets, for oral use Prescribing Information. 2022.

Available at:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2022/203985s023\\_022334s051lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/203985s023_022334s051lbl.pdf). Accessed April 17, 2024.

259. 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>.

260. 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.

261. 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>.

262. 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>.