

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

# **Kidney Cancer**

Version 3.2022 — November 4, 2021

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 Kidney Cancer

NCCN Guidelines Index Table of Contents Discussion

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NCCN Guidelines Version 3.2022 Comprehensive **Kidney Cancer** 

**NCCN** Guidelines Index **Table of Contents** Discussion

**NCCN Kidney Cancer Panel Members** Summary of the Guidelines Updates

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**Kidney Cancer** Initial Workup (KID-1) Primary Treatment and Follow-Up for Stage I-III (KID-1) Primary Treatment for Stage IV (KID-2) Relapse or Stage IV Disease Treatment (KID-3)

Principles of Surgery (KID-A) Follow-up (KID-B) Principles of Systemic Therapy for Relapse or Stage IV Disease (KID-C) Risk Models to Direct Treatment (KID-D)

Hereditary Renal Cell Carcinoma Criteria for Further Genetic Risk Evaluation for Hereditary RCC Syndromes (HRCC-1) Hereditary RCC Syndromes Overview (HRCC-2) Genetic Testing (GENE-1) Kidney-Specific Screening Recommendations for Patients with Confirmed Hereditary RCC (HRCC-B) Kidney-Specific Surgical Recommendations for Patients with Confirmed Hereditary RCC (HRCC-C) Kidney-Specific Systemic Therapy for Patients with Confirmed Hereditary RCC (HRCC-D)

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

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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.

Staging (ST-1)

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2021.

National Comprehensive	NCCN Guidelines Version 3.2022
Cancer Network®	Kidney Cancer

NCCN Guidelines Index **Table of Contents** Discussion

Updates in Version 3.2022 of the NCCN Guidelines for Kidney Cancer from Version 2.2022 include: MS-1

The Discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 2.2022 of the NCCN Guidelines for Kidney Cancer from Version 1.2022 include: HRCC-D

- Kidney Specific Systemic Therapy for Patients with Confirmed Hereditary RCC
- For HLRCC, erlotinib plus bevacizumab will be a category 2A, Useful in Certain Circumstances recommendation.
- For TSC, everolimus will be a category 2A, Useful in Certain Circumstances recommendation.
- > For VHL, belzutifan was added as a category 2A, Preferred Regimen recommendation; pazopanib will be a category 2A, Useful in Certain Circumstances recommendation.

Updates in Version 1.2022 of the NCCN Guidelines for Kidney Cancer from Version 4.2021 include: KID-1

- Primary Treatment
- Stage 1 revised: Radical nephrectomy (in select patients) if nephron-sparing not indicated or feasible)
- Footnote a revised: Imaging with and without contrast....
- Footnote e new: Stereotactic body radiotherapy (SBRT) may be considered for medically inoperable patients with Stage I kidney cancer (category 2B) or with Stage II/III kidney cancer (both category 3)

#### **KID-A**

- Principles of Surgery
- Bullet 3 revised: ....for patients with resectable...

#### KID-C. 1 of 2

Principles of Systemic Therapy

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- First-Line Therapy for Clear Cell Histology:
  - ♦ Favorable Risk. Preferred Regimens
    - Axitinib + pembrolizumab (changed from category 2A to category 1)
    - Pazopanib moved to Other Recommended Regimens;
    - Sunitinib moved to Other Recommended Regimens;
    - Useful in Certain Circumstances
    - High-dose IL-2 (changed from category 2A to category 2B)
  - ◊ Poor/Intermediate Risk, Useful in Certain Circumstances
    - High-dose IL-2 (changed from category 2A to category 3)
  - Temsirolimus (changed from category 2A to category 3)
- Subsequent Therapy for Clear Cell Histology
  - ♦ Preferred Regimens
    - Ipilimumab + nivolumab moved to Other Recommended Regimens
    - Lenvatinib + everolimus (category 1) moved from Other Recommended Regimens
  - ♦ Other Recommended Regimens
    - Everolimus moved to Useful in Certain Circumstances
    - Cabozantinib + nivolumab added
  - Lenvatinib + pembrolizumab added
  - **Our Contrainer** Our Contrainer Contraction Contractions of the Contraction Co
    - Sorafenib changed from category 2A to category 3

• Footnote c revised: 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. Harrison MR, et al. Active surveillance of metastatic renal cell carcinoma: Results from a prospective observational study (MaRCC). Cancer. 2021 Mar 25. Bex A. Increasing the evidence for surveillance of metastatic renal cancer. Cancer. 2021 Mar 25.

#### **KID-C**, 2 of 2

- Principles of Systemic Therapy
- Systemic Therapy for Non-Clear Cell Histology O Preferred regimens: Cabozantinib moved from Other Recommended Regimens
  - ♦ Other Recommended Regimens:
    - Everolimus moved to Useful in Certain Circumstances
    - Nivolumab moved from Useful in Certain Circumstances
    - Pembrolizumab added
  - Our Useful in Certain Circucmstances:
    - Revised Bevacizumab .... and renal cell cancer carcinoma (HLRCC)associated RCC

#### HRCC-2

- Hereditary RCC Syndromes Overview
- Column 2 heading changed: Common Histologyies
- Birt-Hogg-Dubé syndrome (BHDS)/FLCN gene: Under Common Histologies, revised oncocytomaic tumors, papillary RCC
- Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome/SDHA/ B/C/D genes: Under Inheritance Pattern, removed benign lung lesions
- HRCC-A
- Table 2
  - Adrenal or parapanglioma Pheochromocytomas



- <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> If metastatic disease is present or the patient cannot tolerate ureteroscopy.



- patients with Stage I kidney cancer (category 2B), with Stage II/III kidney cancer (both category 3).
- <sup>f</sup>See Follow-up (KID-B).
- <sup>g</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.



<sup>d</sup> See Principles of Surgery (KID-A).

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



<sup>h</sup> Best supportive care can include palliative RT, bisphosphonates, or RANK ligand inhibitors for bony metastases.

and

Best supportive care<sup>h</sup>

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Cancer Network®	Kidney Cancer		

**NCCN** Guidelines Index **Table of Contents** Discussion

#### PRINCIPLES OF SURGERY

- Nephron-sparing surgery (partial nephrectomy) is appropriate in selected patients, for example:
- Unilateral stage I–III tumors where technically feasible

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- 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 is recommended 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 (eq, cryosurgery, radiofrequency ablation) is an option for the management of patients with clinical stage T1 renal lesions.
- Thermal ablation is an option for masses <3 cm, but may also be an</p> option for larger masses in select patients. Ablation in masses >3 cm is associated with higher rates of local recurrence/persistence and complications.
- Biopsy of small lesions confirms a diagnosis of malignancy for surveillance, cryosurgery, and radiofrequency ablation strategies.
- Ablative techniques are associated with a higher local recurrence rate than conventional surgery and may require multiple treatments to achieve the same local oncologic outcomes.<sup>a,b</sup>

- Active surveillance is an option for the initial management of patients with clinical stage T1 renal lesions, for example:
- > Patients with small 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 (≤4 cm) that have a predominantly cystic component is recommended.
- Patients with clinical stage T1 masses and significant competing risks of death or morbidity from intervention.
- Active surveillance entails serial abdominal imaging with timely intervention should the mass demonstrate changes (eg, increasing tumor size, growth rate, infiltrative pattern) indicative of increasing metastatic potential.
- Active surveillance should include periodic metastatic survey including blood work and chest imaging, particularly if the mass demonstrates growth.
- · Generally, patients who would be candidates for cytoreductive nephrectomy prior to systemic therapy have:
- Excellent performance status (ECOG PS <2)</li>
- No brain metastasis

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

National Comprehensive	NCCN Guidelines Version 3.2022
Cancer Network®	Kidney Cancer

NCCN Guidelines Index **Table of Contents** Discussion

#### FOLLOW-UP<sup>a,b</sup> (category 2B)

Stage I (T1a)

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Follow-up During Active Surveillance<sup>c</sup>

- H&P annually
- · Laboratory tests annually, as clinically indicated
- Abdominal imaging:
- Abdominal CT or MRI with contrast if no contraindication within 6 mo 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 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>c</sup>

- H&P annually
- Laboratory tests annually, as clinically indicated
- Abdominal imaging:
- Abdominal CT or MRI with and without IV contrast at 1–6 mo following ablative therapy unless otherwise contraindicated, then CT or MRI (preferred), or US annually for 5 y or longer as clinically indicated. If patient is unable to receive IV contrast, MRI is the preferred imaging modality
- > If there is imaging or clinical concerns for recurrence, then more frequent imaging, renal mass biopsy, or further treatment may be indicated
- Chest imaging:
- Chest x-ray or CT annually for 5 y for patients who have biopsy-proven low-risk renal cell carcinoma (RCC), nondiagnostic biopsies, or no prior biopsy
- <sup>a</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>b</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 (See KID-B, 5 of 5). Further study is required to define optimal follow-up duration.
- <sup>c</sup> Imaging with contrast when clinically indicated.

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

National Comprehensive	NCCN Guidelines Version 3.2022
Cancer Network®	Kidney Cancer

**NCCN** Guidelines Index **Table of Contents** Discussion

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

Stage I (pT1a) and (pT1b)<sup>c</sup>

Follow-up After a Partial or Radical Nephrectomy

H&P annually

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- Laboratory tests annually, as clinically indicated
- Abdominal imaging:
- → Baseline abdominal CT or MRI (preferred), or US within 3–12 mo of surgery, then annually for 3 y or longer as clinically indicated
- > A more rigorous imaging schedule or technique modality can be considered if positive margins or adverse pathologic features (such as sarcomatoid, high-grade [grade 3/4])

Chest imaging:

- Chest x-ray or CT annually for at least 5 y, then as clinically indicated
- A more rigorous imaging schedule or technique modality can be considered if positive margins or adverse pathologic features

<sup>a</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>b</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 (See KID-B, 5 of 5). Further study is required to define optimal follow-up duration.

<sup>c</sup> Imaging with contrast when clinically indicated.

National Comprehensive	NCCN Guidelines Version 3.2022
Cancer Network®	Kidney Cancer

**NCCN** Guidelines Index **Table of Contents** Discussion

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

#### Follow-up for Stage II or III

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- H&P every 3-6 mo for 3 y, then annually up to 5 y, and as clinically indicated thereafter
- Comprehensive metabolic panel and other tests as indicated every 3-6 mo for 3 y, then annually up to 5 y, and as clinically indicated thereafter
- Abdominal imaging:
- ▶ Baseline abdominal CT or MRI within 3–6 mo, then CT or MRI (preferred), or US (US is category 2B for stage III), every 3-6 mo for at least 3 y and then annually up to 5 y
- Imaging beyond 5 y: as clinically indicated

Chest imaging:

- → Baseline chest CT within 3–6 mo with continued imaging (CT preferred) every 3–6 mo for at least 3 y and then annually up to 5 y
- Imaging beyond 5 y: 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> Donat SM. Diaz M. Bishoff JT. et al. Follow-up for clinically localized renal neoplasms: AUA Guideline, J Urol 2013;190:407-416. <sup>b</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 (See KID-B, 5 of 5). Further study is required to define optimal follow-up duration.

National Comprehensive	NCCN Guidelines Version 3.2022
Cancer Network®	Kidney Cancer

**NCCN** Guidelines Index **Table of Contents** Discussion

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

#### Follow-up After Adjuvant Therapy

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

#### Follow-up for Relapsed or Stage IV and Surgically Unresectable Disease<sup>c,d</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 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>c</sup> Imaging with contrast when clinically indicated.

<sup>d</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.

National Comprehensive	NCCN Guidelines Version 3.2022
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**NCCN** Guidelines Index **Table of Contents** Discussion

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

Long-Term Follow-Up (>5 y)

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- 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 to evaluate development of metastatic disease or sequelae of treatment.
- Laboratory tests should be performed annually in surgical patients to evaluate renal function and determine glomerular filtration rate. • Imaging:
- Abdominal imaging may continue beyond recommended follow-up with increasing intervals given low but significant risk of metachronous tumors and/or late recurrences.
- Consider chest imaging for higher stage disease and increasing intervals given low but significant risk of late recurrence.

#### REFERENCES

Active Surveillance

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

Gupta M, Alam R, Patel HD, Semerjian A, et al. Use of delayed intervention for small renal masses initially managed with active surveillance. Urol Oncol 2019;37:18-25. Kassiri B, Cheaib JG, Pierorazio PM. Patients with small renal masses undergoing active surveillance: Is yearly chest imaging necessary? J Urol 2019;201:1061-1063. Chandrasekar T, Ahmad AE, Fadaak K, et al. Natural history of complex renal cysts: Clinical evidence supporting active surveillance. J Urol 2018;199:633-640. Jewett MA, Mattar K, Basiuk J, et al. Active surveillance of small renal masses: progression patterns of early stage kidney cancer. Eur Urol 2011;60:39-44. Ablation

Lay AH, Faddegon S, Olweny EO, et al. Oncologic efficacy of radio frequency ablation for small renal masses: Clear cell vs papillary subtype. J Urol 2015;194:653-657. Beksac AT, Rivera-Sanfeliz G, Dufour CA, et al. Impact of tumor histology and grade on treatment success of percutaneous renal cryoablation. World J Urol 2017:35:633-640.

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

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

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

Long-Term Follow-Up

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

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

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

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

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NCCN Guidelines Index Table of Contents Discussion

#### PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE T	HERAPY FOR CLEAR CELL HISTOLOGY		
Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable <sup>a</sup>	<ul> <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> </ul>	<ul> <li>Axitinib + avelumab<sup>b</sup></li> <li>Cabozantinib (category 2B)</li> <li>Ipilimumab + nivolumab<sup>b</sup></li> <li>Pazopanib</li> <li>Sunitinib</li> </ul>	<ul> <li>Active surveillance<sup>c</sup></li> <li>Axitinib (category 2B)</li> <li>High-dose IL-2<sup>d</sup> (category 2B)</li> </ul>
Poor/ intermediate <sup>a</sup>	<ul> <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>	• Axitinib + avelumab <sup>b</sup> • Pazopanib • Sunitinib	<ul> <li>Axitinib (category 2B)</li> <li>High-dose IL-2<sup>d</sup> (category 3)</li> <li>Temsirolimus<sup>e</sup> (category 3)</li> </ul>

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY			
Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances	
<ul> <li>Cabozantinib (category 1)</li> <li>Lenvatinib + everolimus (category 1)</li> <li>Nivolumab<sup>b</sup> (category 1)</li> </ul>	<ul> <li>Axitinib (category 1)</li> <li>Axitinib + pembrolizumab<sup>b</sup></li> <li>Cabozantinib + nivolumab<sup>b</sup></li> <li>Ipilimumab + nivolumab<sup>b</sup></li> <li>Lenvatinib + pembrolizumab<sup>b</sup></li> <li>Pazopanib</li> <li>Sunitinib</li> <li>Tivozanib<sup>g</sup></li> <li>Axitinib + avelumab<sup>b</sup> (category 3)</li> </ul>	<ul> <li>Everolimus</li> <li>Bevacizumab<sup>f</sup> (category 2B)</li> <li>High-dose IL-2 for selected patients<sup>d</sup> (category 2B)</li> <li>Sorafenib (category 3)</li> <li>Temsirolimus<sup>e</sup> (category 2B)</li> </ul>	

<sup>a</sup> <u>See Risk Models to Direct Treatment (IMDC criteria or MSKCC Prognostic Model) (KID-D)</u>.

- <sup>b</sup> <u>See NCCN Guidelines for Management of Immunotherapy-Related</u> <u>Toxicities</u>.
- <sup>c</sup> Rini BI, et al. Lancet Oncol 2016;17:1317-1324. Harrison M, et al. Cancer 2021;127(13):2204-2212. Bex A. Cancer 2021;127:2184-2186.

included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium >10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-2281. <sup>f</sup> An FDA-approved biosimilar is an appropriate substitute for bevacizumab. <sup>g</sup> For patients who received ≥2 prior systemic therapies.

<sup>e</sup> The poor risk model used in the global ARCC trial to direct treatment with temsirolimus

<sup>d</sup> Patients with excellent performance status and normal organ function.

National Comprehensive	NCCN Guidelines Version 3.202
Cancer Network®	Kidney Cancer

NCCN Guidelines Index **Table of Contents** Discussion

#### PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

2

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY <sup>h</sup>			
Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances	
• Clinical trial • Cabozantinib • Sunitinib	• Lenvatinib + everolimus • Nivolumab <sup>b</sup> • Pembrolizumab <sup>b</sup>	<ul> <li>Axitinib</li> <li>Bevacizumab<sup>f</sup></li> <li>Bevacizumab<sup>f</sup> + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated RCC (<u>See HRCC-D</u>)</li> <li>Bevacizumab<sup>f</sup> + everolimus</li> <li>Erlotinib</li> <li>Everolimus</li> <li>Pazopanib</li> <li>Temsirolimus<sup>e</sup> (category 1 for poor-prognosis risk group; category 2A for other risk groups)</li> </ul>	

<sup>b</sup> See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

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

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

<sup>h</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 (Roubaud G, et al. Oncology 2011;80:214-218; Shah AY, et al. BJU Int 2017;120:782-792). Oral targeted therapies generally do not produce responses in patients with renal medullary carcinoma. Outside of clinical trials, platinum-based chemotherapy regimens should be the preferred therapy for renal medullary carcinoma.

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

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NCCN Guidelines Index Table of Contents Discussion

#### **RISK MODELS TO DIRECT TREATMENT**

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

#### Prognostic factors

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

Prognostic risk groups

- 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>b</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>a</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>b</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 factortargeted agents: Results from a large, multicenter study. J Clin Oncol 2009;27:5794-5799.

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



<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> Tumors that show loss of staining for 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;188:2063-71; 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.)

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

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NCCN Guidelines Index Table of Contents Discussion

#### HEREDITARY RCC SYNDROMES OVERVIEW

Syndrome/Gene	Common Histologies	Inheritance Pattern Major Clinical Manifestations	Other Specialists Involved in Screening
von Hippel-Lindau (VHL)/ <i>VHL</i> gene	Clear cell	<ul> <li>Autosomal dominant</li> <li>See Table 2</li> </ul>	<ul> <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	Type 1 papillary	<ul> <li>Autosomal dominant</li> <li>Multifocal, bilateral renal cell tumors</li> </ul>	Nephrology
Birt-Hogg-Dubé syndrome (BHDS)/ <i>FLCN</i> gene <sup>d,e</sup>	Chromophobe, hybrid oncocytic tumors, papillary RCC	<ul> <li>Autosomal dominant</li> <li>Cutaneous fibrofolliculoma or trichodiscoma, pulmonary cysts, and spontaneous pneumothorax</li> </ul>	<ul><li>Pulmonology</li><li>Dermatology</li></ul>
Tuberous sclerosis complex (TSC)/ <i>TSC1,</i> <i>TSC2</i> genes	Angiomyolipoma, clear cell	<ul> <li>Autosomal dominant</li> <li>See Table 1</li> </ul>	<ul><li>Neurology</li><li>Dermatology</li></ul>
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)/ <i>FH</i> gene	HLRCC or FH-associated RCC/ type 2 papillary	<ul> <li>Autosomal dominant</li> <li>Leiomyomas of skin and uterus, unilateral, solitary, and aggressive renal cell tumors. PET- positive adrenal adenomas</li> </ul>	<ul><li>Gynecology</li><li>Dermatology</li></ul>
<i>BAP1</i> tumor predisposition syndrome (TPDS)/ <i>BAP1</i> gene <sup>f,g</sup>	Clear cell, chromophobe	<ul> <li>Autosomal dominant</li> <li>Melanoma (uveal and cutaneous), kidney cancer, mesothelioma</li> </ul>	<ul> <li>Dermatology</li> <li>Ophthalmology</li> <li>Thoracic oncology</li> </ul>
Hereditary paraganglioma/ pheochromocytoma (PGL/ PCC) syndrome/ <i>SDHA/B/</i> <i>C/D</i> genes	Clear cell (not usually <i>SDHB</i> ), chromophobe, papillary type 2, renal oncocytoma, oncocytic neoplasm	<ul> <li>Autosomal dominant</li> <li>Head and neck paraganglioma and adrenal or extra-adrenal pheochromocytomas, GIST tumors</li> </ul>	<ul> <li>Endocrine</li> <li>Endocrine surgery</li> </ul>

See GENE-1

<sup>d</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>e</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>f</sup> Peña-Llopis S, Vega-Rubín-de-Celis S, Liao A. BAP1 loss defines a new class of renal cell carcinoma. Nat Genet 2012;44:751-759.

<sup>9</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.



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

Comprehensive NCCN Guidelines Version 3.2022 Hereditary Renal Cell Carcinoma

NCCN Guidelines Index **Table of Contents** Discussion

Table 1: Features of Tuberous Sclerosis (TSC)

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Major Features	Minor Features
<ul> <li>Renal angiomyolipoma (AML)<sup>1,2</sup></li> <li>Cardiac rhabdomyoma</li> <li>Cortical dysplasias, including tubers and cerebral white matter migration lines</li> <li>Angiofibromas (≥3) or fibrous cephalic plaque</li> <li>Hypomelanotic macules (3 to &gt;5 mm in diameter)</li> <li>Lymphangioleiomyomatosis (LAM)<sup>1</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 (≥2)</li> </ul>	<ul> <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 (&gt;3)</li> <li>Intraoral fibromas (≥2)</li> <li>Nonrenal hamartomas</li> <li>Retinal achromic patch</li> </ul>

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

Major Features	Minor Features
Hemangioblastomas of the retina, spine, or brain	Endolymphatic sac tumors
Clear cell RCC (ccRCC) diagnosed <40 years of age or multiple/	<ul> <li>Papillary cystadenomas of the epididymis or broad ligament</li> </ul>
bilateral ccRCC tumors diagnosed at any age	<ul> <li>Pancreatic serous cystadenoma (&gt;1)</li> </ul>
Pheochromocytomas	<ul> <li>Pancreatic neuroendocrine tumor or multiple pancreatic cysts (&gt;1)</li> </ul>
Paraganglioma of abdomen, thorax, or neck	
Retinal angiomas	

<sup>1</sup> The combination of AML and LAM does not meet criteria for definite diagnosis.

<sup>2</sup> Multiple AMLs are a major feature.

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NCCN Guidelines Index Table of Contents Discussion

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

#### <u>General</u>

- Follow-up should be individualized based on treatment schedules, side effects, comorbidities, and symptoms.
- Whenever possible, screening should be coordinated with other specialist involved in patient's care.
- Women 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 y 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 <u>HRCC-C</u>; for systemic therapy, see <u>HRCC-D</u>.

#### BAP1-TPDS

Abdominal MRI (preferred) or CT with and without IV contrast every 2 y starting at age 30 y<sup>1</sup>

#### <u>BHDS</u>

• Abdominal MRI (preferred) or CT with and without IV contrast every 3 y starting at age 20 y<sup>2</sup>

#### HLRCC

• Abdominal MRI (preferred) or CT with and without IV contrast annually starting at age 8–10 y<sup>3</sup>

#### <u>HPRC</u>

Abdominal MRI (preferred) or CT with and without IV contrast every 1–2 y starting at age 30 y<sup>4,5</sup>

#### PGL/PCC

• Abdominal MRI (preferred) or CT with and without IV contrast every 4–6 y starting at age 12 y<sup>5,6,8</sup>

#### <u>tsc</u>

• Abdominal MRI (preferred) or CT with and without IV contrast every 3–5 y starting at age 12 y<sup>7</sup>

#### <u>VHL</u>

• Abdominal MRI (preferred) or CT with and without IV contrast to assess kidneys, pancreas, and adrenals every 2 y starting at age 15 y<sup>5</sup>

#### References on HRCC-B 2 of 2

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

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Comprehensive NCCN Guidelines Version 3.2022 Hereditary Renal Cell Carcinoma

**NCCN** Guidelines Index **Table of Contents** Discussion

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

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- <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> 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>8</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.

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NCCN Guidelines Index Table of Contents Discussion

#### 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 pheochromocytomas and should have blood and/or urine screening for this prior to any surgical procedure.

#### **BAP1-TPDS**

No specific guidelines in surgical management for this syndrome (See 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>

#### <u>tsc</u>

- AML 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.

#### <u>VHL</u>

- Management of localized renal masses in patients with VHL are 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 management 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 HRCC-C 2 of 2

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

National Comprehensive	NCCN Guidelines Version 3.2022
Cancer Network®	Hereditary Renal Cell Carcinoma

National

NCCN

**NCCN** Guidelines Index **Table of Contents** Discussion

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

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<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 2014:13:6376-44.

<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 C, Sanda M. 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.



Comprehensive NCCN Guidelines Version 3.2022 Hereditary Renal Cell Carcinoma

**NCCN** Guidelines Index **Table of Contents** Discussion

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

<u>Syndrome</u>	Kidney-Specific Systemic Therapy
HLRCC	Useful in Certain Circumstances <ul> <li>Erlotinib plus bevacizumab<sup>1,2</sup></li> </ul>
TSC	Useful in Certain Circumstances <ul> <li>Everolimus<sup>3</sup></li> </ul>
VHL	Preferred Regimen • Belzutifan Useful in Certain Circumstances • Pazopanib <sup>4</sup>

<sup>1</sup> An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

- <sup>2</sup> There are no specific FDA-approved therapies for HLRCC. Treatment with erlotinib plus bevacizumab demonstrated benefit in patients with metastatic RCC from HLRCC. Srinivasan R, Gurram S, Al Harthy M, et al. Results from a phase II study of bevacizumab and erlotinib in subjects with advanced hereditary leiomyomatosis and renal cell cancer (HLRCC) or sporadic papillary renal cell cancer [abstract]. J Clin Oncol 2020 38:15 suppl, 5004-5004.
- <sup>3</sup> Everolimus is an FDA-approved therapy for asymptomatic, growing angiomyolipoma measuring >3 cm in diameter. Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, doubleblind, placebo-controlled trial, Lancet 2013:381:817-824.
- <sup>4</sup> Pazopanib was associated with a >50% objective response rate in renal lesions in a 31-patient phase II study. Jonasch E, McCutcheon IE, Gombos DS, et al. Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-centre, phase 2 trial. Lancet Oncol 2018;19:1351-1359.

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**NCCN** Guidelines Index Table of Contents Discussion

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

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**Primary Tumor** 

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ТΧ	Primary tumor cannot be assessed	Stan	ا م	Т1	NO	MO
Т0	No evidence of primary tumor	Stag		то Т	NO	MO
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney	Stag		12 T1 T2		MO
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney	Slay	je m	11-12 T2		MO
T1b	Tumor >4 cm but ≤7 cm in greatest dimension, limited to the kidney	Star	ie IV	тз т4	Any N	MO
T2	Tumor >7 cm in greatest dimension, limited to the kidney	Olug		Anv T	Any N	M1
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney			, ury i		
T2b	Tumor >10 cm, limited to the kidney					
Т3	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia					
Т3а	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	Table GX	<b>3. His</b> Grade	<b>tologic G</b> e cannot l	rade (G) be assessed	
T3b	Tumor extends into the vena cava below the diaphragm	G1	Nucle	oli absen	t or inconspic	uous and basophilic
T3c	Tumor extends into the vena cava above the diaphragm or invades the wall		at 40	0x magnif	ication	
	of the vena cava	G2	Nucle	oli consp	icuous and eo	sinophilic at 400x
Т4	Tumor invades beyond Gerota's fascia (including contiguous extension into		magr magr	ification, vification	visible but not	prominent at 100x
		G3	Nucle magr	eoli consp nification	icuous and eo	sinophilic at 100x
N I	Degional Lymph Nadaa		-			

Marked nuclear pleomorphism and/or G4 multinucleate giant cells and/or rhabdoid and/or sarcomatoid differentiation

Table 2. AJCC Prognostic Groups

#### Regional Lymph Nodes Ν NX Regional lymph nodes cannot be assessed

- No regional lymph node metastasis N0
- Metastasis in regional lymph node(s) N1
- Μ **Distant Metastasis**
- No distant metastasis M0
- M1 **Distant metastasis**

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

National Comprehensive	NCCN Guidelines Version 3.2022
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	NCCN Categories of Evidence and Consensus
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

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#### **NCCN Guidelines Version 3.2022** Comprehensive Cancer **Kidney Cancer**

Discussion This discussion corresponds to the NCCN Guidelines for Kidney Cancer. Last updated: November 4, 2021.

#### **Table of Contents**

NCCN

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OverviewMS-2
Literature Search Criteria and Guidelines Update Methodology MS-2
Initial Evaluation and StagingMS-3
Treatment of Localized DiseaseMS-3
Management of Stage I (T1a) Disease MS-5
Management of Stage I (T1b) Disease MS-5
Management of Stage II and III Disease MS-6
Follow-up After Treatment of Localized Disease MS-6
Management of Relapsed or Stage IV DiseaseMS-8
Surgical Options for Patients with Relapsed or Stage IV Disease MS-8
Systemic Therapy Options for Patients with Relapsed or Stage IV DiseaseMS-10
Systemic Therapy for Patients with Clear Cell RCC (ccRCC) MS-10
Systemic Therapy for Patients with Non-Clear Cell RCC (nccRCC) MS-16
Follow-up Recommendations for Relapsed or Stage IV Disease and Surgically Unresectable Disease

Supportive Care MS-20
Hereditary RCC Syndromes MS-21
Genetic Testing and Surveillance Recommendations for Patients with a Personal or Family History of an RCC SyndromeMS-21
Genetic Testing and Screening Recommendations for Patients with a Clinical Diagnosis of RCC Who Have Characteristics Consistent with Inherited RCCMS-22
Kidney-Specific Surgical Recommendations for Patients with a Confirmed Hereditary RCC SyndromeMS-22
Kidney-Specific Systemic Therapy for Patients with Confirmed Hereditary RCCMS-22
Data Summary MS-23
Table 1: Key Studies on First-Line Therapy for Patients with Clear Cell RCC (ccRCC)MS-24
Table 2: Key Studies on Subsequent Therapy for Patients with Clear Cell         RCC (ccRCC)         MS-28
Table 3: Key Studies on Systemic Therapy for Patients with Non-Clear Cell         RCC (nccRCC)MS-31
ReferencesMS-33

#### Overview

NCCN

An estimated 76,080 Americans will be diagnosed with cancers of the kidney and renal pelvis and 13,780 will die of the disease in the United States in 2021.<sup>1</sup> Renal cell carcinoma (RCC) comprises approximately 3.8% of all new cancers, with a median age at diagnosis of 64 years.<sup>2</sup> Approximately 85% of kidney tumors are RCC, and approximately 70% of these have a clear cell histology (ccRCC).<sup>3-5</sup> Other less common cell types include papillary, chromophobe, translocation, and Bellini duct (collecting duct) tumors.<sup>6</sup> Medullary renal carcinoma is a rare and aggressive RCC variant that almost exclusively arises in patients who are sickle-cell trait positive.<sup>7</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 to ccRCC and other proliferative vascular lesions.<sup>8-11</sup> (Also see the <u>Hereditary RCC Syndromes section</u> 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 0.7% each year from 2006 through 2015.<sup>2</sup> The 5-year survival rate for localized RCC has increased from 88.4% (during 1992–1995) to 92.6% (during 2007–2013) and for advanced disease from 7.3% (during 1992–1995) to 11.7% (during 2007–2013).<sup>12</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>13-22</sup> RCC primarily metastasizes to the lung, bone, liver, lymph nodes, adrenal gland, and brain.<sup>9,23,24</sup>

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

#### Literature Search Criteria and Guidelines Update Methodology

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

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

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

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

#### 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>25,26</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>27</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 chest x-ray are essential studies in the initial workup.<sup>28</sup> For metastatic evaluation, at the very least, chest radiography must be performed, although chest CT is more accurate than chest radiograph for chest staging.<sup>29,30</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>31,32</sup> All imaging studies should be performed with and without contrast, such as renal protocol.

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

Most bone and brain metastases are symptomatic at diagnosis. Therefore, a bone scan is not routinely performed unless the patient has an elevated serum alkaline phosphatase (ALP) or complains of bone pain.<sup>33</sup> CT or 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 results show clear findings in the imaging studies. In selected individuals, needle biopsy may be considered for small lesions to establish diagnosis of RCC and guide active surveillance strategies, cryosurgery, radiofrequency, and ablation strategies.<sup>34</sup> As noted above, biopsy should also be considered if a central lesion or a homogeneous infiltration of renal parenchyma is observed on scans to rule out urothelial carcinoma or lymphoma, respectively.

The value of PET in RCC remains to be determined. Currently, PET alone is not a tool that is standardly used to diagnose kidney cancer or follow for evidence of relapse after nephrectomy.<sup>35</sup>

If patients present with multiple renal masses, are 46 years old or younger at diagnosis, or have a family history of RCC, they should consider genetic evaluation (see the <u>Hereditary RCC Syndromes section</u> 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 own 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>36-43</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>44-49</sup> Radical nephrectomy can lead to an increased risk for chronic kidney disease<sup>50,51</sup> and is associated with increased risks of cardiovascular morbidity and mortality according to population-based studies.<sup>52</sup> When compared with radical nephrectomy, partial nephrectomy can achieve preserved renal function, decreased overall mortality, and reduced frequency of cardiovascular events.<sup>52-56</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,  $\leq$ 7 cm in greatest dimension) and a normal contralateral kidney, with equivalent outcomes to radical nephrectomy.<sup>47,57-59</sup> Radical nephrectomy should not be employed when nephron sparing can be achieved. A more recent study showed that among Medicare beneficiaries with early-stage kidney cancer, treatment with partial rather than radical nephrectomy was associated with improved survival.<sup>60</sup>

Studies with limited follow-up data show that the oncologic outcome for laparoscopic versus open nephron-sparing surgery appears to be similar.<sup>61,62</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>63</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>64</sup> However, in some patients with localized RCC, nephron-sparing surgery may not be suitable because of locally advanced tumor growth or because 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 OS, time to progression of disease, or progression-free survival (PFS) between the two study groups.<sup>65</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>66</sup> Assessment of lymph node status is based on enlargement of imaging (CT/MRI) and on assessment by direct palpation at time of surgery. CT/MRI may not detect small metastases in normal lymph nodes.<sup>67</sup>

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

#### Adrenalectomy

Ipsilateral adrenal gland resection should be considered for patients with large upper pole tumors or abnormal-appearing adrenal glands on CT.<sup>68-70</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>71</sup>

#### Active Surveillance and Ablative Techniques

Active surveillance<sup>72,73</sup> is defined as the initial monitoring of tumors using abdominal imaging techniques with delayed intervention when indicated. Elderly patients and those with small renal masses (<2 cm) and other comorbidities often have a low RCC-specific mortality.<sup>74</sup> Active surveillance and ablative techniques such as cryotherapy or radiofrequency ablation are alternative strategies for selected patients, particularly the elderly and those with competing health risks.

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

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

#### Management of Stage I (T1a) Disease

The Panel prefers surgical excision by partial nephrectomy for the management of clinical stage I (T1a) renal masses. Adequate expertise and careful patient selection are important. Partial nephrectomy is most appropriate in patients with small unilateral 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. 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, and, if required, treat for progression.<sup>72</sup>

Although distant recurrence-free survival rates of ablative techniques and conventional surgery are comparable, ablative techniques have been associated with an increased risk of local recurrence.<sup>75-78</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 (T1a) RCC.

#### Management of Stage I (T1b) Disease

Partial nephrectomy for localized RCC has an oncologic outcome similar to that of radical surgery for T1b tumors.<sup>79,80</sup> Surgery by partial nephrectomy, whenever feasible, or by radical nephrectomy is the standard of care for clinical T1b tumors according to the NCCN Kidney Cancer Panel. Select patients may be managed by active surveillance.

#### Management of Stage II and III Disease

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The curative therapy for patients with stages II and III disease remains radical nephrectomy.<sup>42</sup> Radical nephrectomy is the preferred treatment for the tumors that extend into the inferior vena cava. Resection of a caval or atrial thrombus often requires the assistance of cardiovascular surgeons because treatment-related mortality may reach 10%, depending on the local extent of the primary tumor and the level of vena caval extension. Partial nephrectomy is generally not suitable for patients with locally advanced tumors; however, they 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, adjuvant treatment after nephrectomy has no established role in patients who have undergone a complete resection of their tumor. An exception is for patients with stage III disease, clear cell histology, and a high risk for relapse. These patients may be treated with adjuvant sunitinib (category 3) for 1 year. However, several clinical trials (ie, ASSURE, ATLAS, PROTECT) tested sunitinib and additional targeted therapies in the adjuvant setting, which did not show a clinical benefit.<sup>81-83</sup> Eligible patients should be offered enrollment in randomized clinical trials. Adjuvant radiation therapy after nephrectomy has not shown benefit, even in patients with nodal involvement or incomplete tumor resection.

In contrast, the phase III S-TRAC trial was the first to show a benefit in DFS with adjuvant treatment following nephrectomy in RCC. 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 adverse events (AEs) occurred in 63.4% of patients treated with sunitinib compared to 21.7% of those on placebo.<sup>84</sup> Median OS had not been reached in the sunitinib or placebo groups in either of these publications.<sup>84,85</sup>

The Panel discussed including sunitinib as an option for adjuvant therapy in patients at high risk for recurrence based on the DFS benefit demonstrated in the S-TRAC trial. Due to concerns from some Panel members about toxicity, lack of a demonstrated OS benefit, and conflicting results between the S-TRAC trial and the ASSURE/ATLAS/PROTECT trials, there was not uniform consensus that this intervention is appropriate, leading to a category 3 recommendation.

#### 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>86</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 of a 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>87</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>88</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 T1a

For follow-up during active surveillance, the Panel recommends an annual history and physical examination and annual laboratory tests as clinically indicated. In order to study the growth rate of the tumor, the Panel recommends abdominal imaging (CT or MRI with contrast) within 6 months for 2 years 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>89</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 for pulmonary metastases. The Panel notes that follow-up may be individualized based on surgical status, treatment schedules, side effects, comorbidities, and symptoms.

#### Follow-up After Ablative Therapy for Stage T1a

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

For those who have biopsy-proven low-risk 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–III

For patients with stages pT1a and pT1b who underwent a partial or radical nephrectomy, the Panel recommends an annual history and physical examination and annual laboratory tests as clinically indicated. The Panel recommends a baseline abdominal CT, MRI (preferred), or US within 3 to 12 months following renal surgery, then annually for 3 years or longer as clinically indicated. A more rigorous imaging schedule or modality 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>61,90,91</sup> The Panel also recommends yearly chest x-ray or CT for at least 5 years and as clinically indicated thereafter. As above, a more rigorous imaging schedule or modality can be considered if the patient has positive margins or adverse pathologic features in the patient for smaller tumors.<sup>61,90,91</sup> The Panel also recommends yearly chest x-ray or CT for at least 5 years and as clinically indicated thereafter. As above, a more rigorous imaging schedule or modality can be considered if the patient has positive margins or adverse pathologic features.

For patients with stage II–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 stages pT1a or pT1b. Therefore, for these patients, the Panel recommends a history and physical examination every 3 to 6 months for 3 years, then annually for 5 years. The follow-up evaluation may be extended beyond 5 years at the discretion of the physician as clinically indicated.

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

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

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

Alternate surveillance programs have been proposed, such as the surveillance protocol based on the University of California Los Angeles (UCLA) Integrated Staging System (UISS).<sup>92</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>92</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>93,94</sup>

The first prognostic factor model to be widely applied from the Memorial Sloan Kettering Cancer Center (MSKCC). The model was derived from examining prognostic factors in patients (n = 463) with metastatic RCC enrolled in clinical trials and treated with interferon (IFN).<sup>93</sup> Prognostic factors for multivariable analysis included five variables: interval from diagnosis to treatment of less than 1 year; Karnofsky Performance Status (KPS) less than 80%; serum LDH greater than 1.5 times the upper limit of normal (ULN); corrected serum calcium greater than the ULN; and serum hemoglobin less than the lower limit of normal (LLN). Patients with none of these factors are considered low risk or with good prognosis, those with one or two factors present are considered 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>95</sup>

A prognostic model derived from a population of patients with metastatic RCC treated with vascular endothelial growth factor (VEGF)-targeted therapy has been developed, and is known as the IMDC (International Metastatic RCC Database Consortium) or Heng's model.<sup>94</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 less than 80%, and time from initial diagnosis to initiation of therapy of less than 1 year. Additional, independent, adverse prognostic factors validated in this model are absolute neutrophil count (ANC) greater than ULN and platelets greater than ULN.94

Patients with none of the identified six adverse factors were in the favorable-risk category (n = 133; 22.7%) in which a median overall survival (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>94</sup> This model was validated in an independent dataset.<sup>96</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 for metastatic disease on CT may be hyperplastic and not involved with tumor; thus, the presence of minimal regional adenopathy does not preclude surgery.

Cytoreductive nephrectomy before systemic therapy is recommended in select patients with a potentially surgically resectable primary tumor mass. A retrospective analysis conducted in the cytokine era indicated that patients most likely to benefit from cytoreductive nephrectomy before systemic therapy were those with lung-only metastases, good prognostic features, and good performance status.<sup>97</sup> Retrospective data from the IMDC suggested that cytoreductive nephrectomy continues to play a role in patients treated with VEGF-targeted agents.<sup>98</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.99 The median OS was 18.4 months in the sunitinib-alone group and 13.9 months in the sunitinib after nephrectomy group (hazard ratio [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>99,100</sup> At this point in time 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 or with ablative techniques for selected patients who are not candidates for metastasectomy. Candidates include patients who: 1) initially present with primary RCC and oligometastatic sites; or 2) develop oligometastases after a prolonged disease-free interval from nephrectomy. Oligometastatic sites that are amenable to this approach include the lung, bone, and brain. The primary tumor and the metastases may be resected during the same operation or at different times. Most patients who undergo targeted treatment of oligometastases experience recurrence, but long-term relapse-free survival has been reported in these patients.

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

Patients who have undergone a nephrectomy and years later develop an oligometastatic recurrence also have the option of metastasectomy,
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stereotactic body radiation therapy (SBRT),<sup>101-103</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 tyrosine kinase inhibitors (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. Immune checkpoint inhibitors provided a revolution in treatment options. Checkpoint antibodies alter the interaction between immune cells and antigen-presenting cells, including tumor cells. These agents can augment an anti-tumor immune response and have shown promise in a number of tumor indications.

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

#### NCCN Categories of Preference

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

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

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

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

#### Systemic Therapy for Patients with Clear Cell RCC (ccRCC)

#### ccRCC: First-Line, 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 programmed death-1 (PD-1; expressed on activated T cells) and blocks the interaction between PD-1 and its ligands programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2; both expressed on antigen-presenting cells). In April 2019, the FDA approved axitinib in combination with pembrolizumab for first-line treatment of patients with advanced RCC.<sup>104,105</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 (see <u>Table 1 for efficacy data</u>). Patients received either axitinib/pembrolizumab or sunitinib; those receiving the combination regimen had a significantly higher overall response rate (ORR) and longer PFS than those receiving sunitinib. Median OS was not reached for either group, but the HR favored axitinib/pembrolizumab.<sup>106</sup> A subsequent exploratory analysis with a 31-

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month median followup period agreed with these data.<sup>107</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 cabozantinib in combination with nivolumab for first-line treatment of patients with advanced RCC.<sup>108</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 (see Table 1 for efficacy data). Patients received either cabozantinib/nivolumab or sunitinib; those receiving cabozantinib/nivolumab had significantly longer ORR and PFS than those receiving sunitinib. Median OS was not reached for either group, but the HR favored cabozantinib/nivolumab.<sup>107,109</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-α (PDGFR-α); c-KIT; and RET. Pembrolizumab's mechanism of action was described previously. In August 2021, the FDA approved lenvatinib in combination with pembrolizumab for first-line treatment of patients with advanced RCC.<sup>110</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 (see Table 1 for efficacy data). 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. Median OS was not reached

for either group, but the HR for lenvatinib/pembrolizumab versus sunitinib favored the combination regimen. In contrast, OS was not significantly different between the lenvatinib/everolimus and sunitinib groups.<sup>111</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. The Panel felt that the CLEAR data for lenvatinib/everolimus did not yet support the combination regimen's inclusion in the NCCN Guidelines for Kidney Cancer.

#### 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>112</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>113</sup> The study's coprimary endpoints were ORR, OS, and PFS in intermediate- and poorrisk patients only; exploratory analyses of data in favorable-risk patients were reported separately (see Table 1 and First-line, Other Recommended Regimens for ccRCC). In intermediate-/poor-risk patients, combination ipilimumab/nivolumab led to a higher ORR and CR rate versus sunitinib monotherapy. Median PFS did not meet the prespecified threshold, and was not statistically significant between the two treatment arms. Treatment-related AEs occurred in 93% of patients in the ipilimumab/nivolumab group and 97% of patients in the sunitinib group; grade 3 or 4 events occurred in 46% and 63%, respectively. AEs led to treatment discontinuation in 22% and 12% of patients receiving ipilimumab/nivolumab and sunitinib, respectively. Treatment-related

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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>113</sup> Based on these data, the Panel recommends first-line ipilimumab/nivolumab as a category 1, preferred treatment option for poor- and intermediate-risk patients with ccRCC.

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

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In the open-label, randomized phase II CABOSUN trial, patients with intermediate- or poor-risk advanced RCC received either cabozantinib or sunitinib. <u>See Table 1 for efficacy data</u>. Those treated with cabozantinib showed a significantly increased median PFS and higher ORR compared to those treated with sunitinib. <sup>114</sup> Based on these results, the Panel recommends first-line cabozantinib as a category 2A, preferred treatment option for poor- and intermediate-risk patients with ccRCC.

#### ccRCC: First-Line, Other Recommended Regimens

#### Axitinib with Avelumab (All Risk Groups)

Avelumab is a monoclonal antibody that selectively binds to PD-L1; axitinib's mechanism of action was described previously. In May 2019, the FDA approved axitinib/avelumab for first-line treatment of patients with advanced RCC. Data from the randomized phase III JAVELIN Renal 101 trial, which included patients with favorable-, intermediate-, or poor-risk RCC, supported the combination therapy's approval for this indication (see Table 1 for efficacy data).<sup>115,116</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>115</sup> and 13-month interim<sup>116</sup> analyses. Based on these results, the Panel added first-line axitinib/avelumab as a category 2A, other recommended regimen for patients with ccRCC across all risk groups.

#### Cabozantinib (Favorable-Risk Group)

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

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

The CheckMate 214 trial included favorable-risk patients treated with ipilimumab/nivolumab or sunitinib (see Table 1 for efficacy data). The 18month OS in poor-/intermediate-risk patients favored ipilimumab/nivolumab over sunitinib, but an exploratory analysis of OS data from favorable-risk patients favored sunitinib over the combination regimen. ORR and median PFS were also lower in favorable-risk patients receiving ipilimumab/nivolumab than those receiving sunitinib. However, CR rates were higher in favorable-risk patients than in poor-/intermediaterisk patients, regardless of treatment regimen.<sup>113</sup>

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

#### Pazopanib (All Risk Groups)

Pazopanib is an oral multitargeted TKI/angiogenesis inhibitor of VEGFRs, PDGFR- $\alpha$  and - $\beta$ , and stem cell factor receptor (c-KIT). The drug's safety and efficacy were evaluated in an open-label phase III study. Patients with advanced ccRCC who received 0-1 prior treatments 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>117</sup> but there was no difference in OS between the two groups.<sup>118</sup> Notable grade 3 toxicity was hepatotoxicity, indicated by elevated levels of alanine (30%) and aspartate

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(21%) transaminase.<sup>117</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>119,120</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>121-124</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>121</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>125</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.

## ccRCC: First-Line, 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 treatmentnaïve, asymptomatic, metastatic RCC followed patients on active surveillance through radiographic assessment at defined intervals until a decision was made to initiate systemic therapy.<sup>126</sup> Of the 48 patients included in the analysis, the median time of surveillance from registration to initiation of systemic therapy was 14.9 months. This study demonstrated that a subset of patients with advanced ccRCC can safely undergo active surveillance before starting systemic therapy. Therefore, the Panel included active surveillance as a category 2A, useful in certain circumstances option for select, asymptomatic patients with favorable-risk ccRCC.

## Axitinib (All Risk Groups)

As a second-line therapy for patients with ccRCC, axitinib treatment led to higher ORR and longer median PFS compared with sorafenib.<sup>127</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>128</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>129-131</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 favorable-risk patients and category 3 for poor-/intermediate-risk patients).

## Temsirolimus (Poor-/Intermediate-Risk Patients)

Temsirolimus is an inhibitor of the mTOR protein. The randomized, openlabel phase III ARCC study enrolled previously untreated patients with advanced RCC who had three or more unfavorable prognostic factors.<sup>132</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. Based on these data, the Panel has included first-

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line temsirolimus as a category 3, useful in certain circumstances option for poor- and intermediate-risk patients with ccRCC.

#### ccRCC: Subsequent, Preferred Regimens

#### Cabozantinib

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In the randomized phase III METEOR trial, patients with disease progression after previous TKI therapy receive cabozantinib or everolimus. <u>See Table 2 for efficacy data</u>. Median PFS was significantly longer and ORR significantly higher in patients receiving cabozantinib versus everolimus.<sup>133</sup> The final analysis of the METEOR trial showed a statistically significant increase in OS in the cabozantinib arm versus the everolimus arm.<sup>134</sup>.<sup>134,135</sup>

Additionally, a network meta-analysis comparing the relative effectiveness of subsequent treatment options for RCC found the probability of longer PFS during the analyzed 3 years to be higher with cabozantinib compared to everolimus, nivolumab, axitinib, sorafenib, and best supportive care.<sup>136</sup> Based on these data, the Panel has included cabozantinib as a category 1, preferred subsequent therapy option for patients with ccRCC.

#### 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>137,138</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 singleagent everolimus. <u>See Table 2 for efficacy data</u>. PFS and median OS were significantly longer in patients receiving lenvatinib/everolimus versus everolimus monotherapy.<sup>139,140</sup> Based on these data, the Panel considers lenvatinib/everolimus a category 1, preferred subsequent therapy option for patients with ccRCC.

#### Nivolumab

In the randomized phase III CheckMate 025 trial, patients with advanced ccRCC, who were previously treated with one or more lines of therapy (excluding mTOR inhibitors) received either nivolumab or everolimus. <u>See Table 2 for efficacy data</u>. Patients receiving nivolumab had significantly longer OS and significantly higher ORR than those receiving everolimus.<sup>141</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>142</sup> Based on these data, the Panel has included nivolumab as a category 1, preferred subsequent therapy option for patients with ccRCC.

## ccRCC: Subsequent, Other Recommended Regimens

#### Axitinib

The randomized phase III AXIS study compared second-line axitinib versus sorafenib. <u>See Table 2 for efficacy data</u>. Median PFS was significantly longer and ORR significantly higher in patients receiving axitinib versus sorafenib.<sup>127</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.<sup>143</sup> Based on these data, the Panel included axitinib as a category 1, other recommended subsequent therapy option for patients with ccRCC.

#### Axitinib with Pembrolizumab

Upon axitinib/pembrolizumab's FDA approval in a first-line setting,<sup>104,105</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 published data to support the use of axitinib/pembrolizumab in a second-line setting, they thought that clinicians were likely to consider the

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combination as a treatment option in patients with advanced ccRCC whose disease progressed after first-line sunitinib therapy. Thus, the Panel added axitinib/pembrolizumab as a category 2A, other recommended subsequent therapy option for patients with ccRCC.

#### Cabozantinib with Nivolumab

Apolo et al 2020<sup>144</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>145</sup> reported a pooled analysis of the phase I dose-finding cohort and seven subsequent expansion cohorts, which included 16 patients with metastatic RCC. <u>See Table 2 for efficacy data</u>. In these patients, median OS was 38.6 months (95% CI, 19.4–not estimable [NE]). Based on these data, the Panel considers cabozantinib/nivolumab a category 2A, other recommended subsequent therapy option for patients with ccRCC.

#### 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. <u>See Table 2 for efficacy data</u>. 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>146</sup> Based on these data, the Panel considers ipilimumab/nivolumab a category 2A, other recommended subsequent therapy option for patients with ccRCC.

#### Lenvatinib with Pembrolizumab

The ongoing phase II KEYNOTE-146 trial included 3 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 immune checkpoint

inhibitors, and those who had previously received at least one anti–PD-1 or anti–PD-L1 immune checkpoint inhibitor. <u>See Table 2 for efficacy data</u>. 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>147</sup> Based on these data, the Panel considers lenvatinib/pembrolizumab a category 2A, other recommended subsequent therapy option for patients with ccRCC.

#### Pazopanib

A phase III trial comparing pazopanib with placebo, detailed earlier under the <u>First-line</u>, <u>Other Recommended Regimens for Clear Cell RCC</u>, also included patients who had received prior cytokine therapy. <u>See Table 2 for</u> <u>efficacy data</u>. PFS was significantly longer with pazopanib versus placebo in the treatment-experienced sub-population,<sup>117</sup> but OS was similar between the two groups.<sup>118</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%.<sup>148</sup> Based on these data, the Panel considers pazopanib a category 2A, other recommended subsequent therapy option for patients with ccRCC.

#### 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>122,149</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

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another.<sup>150-154</sup> Sunitinib is considered a category 2A, other recommended subsequent therapy option for patients with ccRCC.

#### Tivozanib

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In March 2021, the FDA approved tivozanib, a multitargeted TKI, for patients with relapsed or refractory advanced RCC who previously received two or more systemic therapies.<sup>155</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; OS was similar between the two groups.<sup>156</sup> Based on these data, the Panel considers tivozanib as a category 2A, other recommended subsequent therapy option for patients with ccRCC.

#### Axitinib with Avelumab

Extrapolating on the first-line JAVELIN Renal 101 data for poor-/intermediate-risk patients (see First-line, Other Recommended Regimens for ccRCC), the Panel added axitinib/avelumab as a category 3, other recommended subsequent therapy option for patients with ccRCC.

#### ccRCC: Subsequent, Useful In Certain Circumstances Regimens

#### **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>157,158</sup> Everolimus is listed as a category 2A, useful in certain circumstances subsequent therapy option for patients with ccRCC.

#### Bevacizumab

Phase II trials have shown benefit of bevacizumab monotherapy after prior treatment with a cytokine.<sup>159</sup> Bevacizumab is a category 2B, useful in certain circumstances subsequent therapy option for patients with ccRCC.

#### 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.

#### 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>160-164</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>165,166</sup> Sorafenib is listed as a category 3, useful in certain circumstances subsequent therapy option for patients with ccRCC.

#### 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. While a significant OS advantage was observed for sorafenib, PFS was similar between the two groups.<sup>167</sup> The Panel considers temsirolimus a category 2B, useful in certain circumstances subsequent therapy option for patients with ccRCC.

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

Clinical trials of targeted agents have predominantly focused on patients with clear cell RCC due to the high prevalence of ccRCC.<sup>168</sup> Data from systematic reviews, meta-analyses, and phase II studies with targeted

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agents also show some activity in patients with nccRCC. Compared with responses in ccRCC, however, the response rates with these agents are significantly lower for nccRCC. Therefore, according to the Panel, enrollment in clinical trials is the preferred strategy for nccRCC.

#### nccRCC: Preferred Regimens

#### Cabozantinib

The randomized phase II SWOG 1500 trial compared the MET-targeted TKIs cabozantinib, crizotinib, and savolitinib with standard-of-care sunitinib in patients with advanced papillary RCC who had previously received up to 1 previous systemic therapy, excluding VEGF- and MET-targeted TKIs. Assignment to the crizotinib and savolitinib arms was halted due to results of a prespecified futility analysis.<sup>169</sup> <u>See Table 3 for efficacy data</u>. Patients receiving cabozantinib had significantly longer PFS and a higher ORR than those receiving sunitinib; however, OS was similar between the two groups. Based on these data, the Panel included cabozantinib as a category 2A, preferred option for patients with nccRCC.

#### Sunitinib

Two recent randomized phase II studies compared first-line sunitinib with first-line everolimus in patients with nccRCC. <u>See Table 3 for efficacy</u> <u>data</u>. While data from the ASPEN trial<sup>170</sup> suggested that patients receiving sunitinib had significantly longer PFS than those receiving everolimus, data from the ESPN trial<sup>171</sup> suggested that both OS and PFS were similar between the two groups.

Additionally, a meta-analysis of randomized clinical trials for patients with nccRCC found that TKI treatment reduced the risk of progression compared with mTOR inhibitors.<sup>172</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, sunitinib is listed as a category 2A, preferred option for patients with nccRCC.

#### nccRCC: Other Recommended Regimens

#### Lenvatinib with Everolimus

Extrapolating on data from the phase III lenvatinib/everolimus trial in patients with ccRCC<sup>139</sup> (see <u>Subsequent, Preferred Regimens for ccRCC</u>), the Panel added the combination therapy as a category 2A, other recommended regimen for patients with nccRCC.

They also reviewed data<sup>173</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 complete response (CR). The median duration of response was not estimable. 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). 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>174</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. A separate retrospective analysis found modest responses with PD-1/PD-L1 inhibitors in 43 patients also with

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metastatic nccRCC.<sup>175</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.

#### 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>176</sup> See <u>Table 3 for efficacy data</u>. The majority (about 72%) of patients had confirmed papillary RCC, about 13% had chromophobe RCC, and about 16% had unclassified RCC histology. ORR across all subtypes was approximately 27% (ORR by histology was 29% for papillary, 10% for chromophobe, and 31% for unclassified). Overall PFS and OS were 4.2 months and 28.9 months, respectively. Based on these data, the Panel added pembrolizumab as a category 2A, other recommended regimen for patients with nccRCC.

#### nccRCC: Useful in Certain Circumstances Regimens

#### Axitinib

A phase II trial of axitinib in 40 patients with recurrent or metastatic nccRCC that failed treatment with temsirolimus found a median PFS of 7.4 months and ORR of 37.5%.<sup>177</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 patients with papillary RCC. The PFS reported for each of these patients was 25, 15, 11, 10, and 6 months. <sup>178</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 (HLRCC)-Associated RCC

HLRCC is a hereditary condition in which affected patients are at risk for development of skin and uterine leiomyomas, as well as an aggressive form of papillary kidney cancer.<sup>179</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>180</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. <sup>180</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>181</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 higher PFS and ORR than other histologies.<sup>182</sup> Based on these data, the Panel recommends bevacizumab plus everolimus as a category 2A, useful in certain circumstances option for patients with nccRCC.

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#### Erlotinib

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The efficacy of erlotinib, an oral epidermal growth factor receptor (EGFR) TKI, was studied in 52 patients with advanced papillary RCC.<sup>183</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.<sup>183</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>184</sup> In a phase II study of treatment-experienced patients with nccRCC,<sup>185</sup> OS was 14 months and PFS was 5.2 months. According to data from the phase II RAPTOR trial,<sup>186</sup> OS and PFS ranged from 24 to 28 months and PFS ranged from 5 to 8 months; patients with type 1 nccRCC had better responses than those with type 2 histology. Based on these data, the Panel included everolimus as a category 2A, useful in certain circumstances option for patients with nccRCC.

#### 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%.<sup>187</sup> A retrospective analysis of an Italian multicenter cohort of nccRCC patients found treatment with pazopanib to be effective and safe.<sup>182</sup> Based on these data, the Panel considers pazopanib a category 2A, useful in certain circumstances option for patients with nccRCC. There is an ongoing clinical trial evaluating the efficacy of second-line pazopanib in patients with nccRCC.188

#### Temsirolimus

A retrospective subset analysis of the global phase III ARCC trial demonstrated benefit of temsirolimus not only in ccRCC but also in nccRCC.<sup>132,189</sup> In patients with nccRCC (predominantly papillary RCC), the median OS was 11.6 months with temsirolimus and 4.3 months with IFNα. 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>190</sup> Temsirolimus is a useful in certain circumstances option for nccRCC; it has a category 1 designation for poor-risk patients and a category 2A designation for favorable-/intermediate-risk patients.

#### Additional Treatment Options for Rare Types of nccRCC

Among the nccRCC histologies, renal medullary carcinoma is extremely rare, comprising approximately 2% of all primary renal tumors in young people.<sup>191,192</sup> Metastatic disease is seen at presentation in 67% to 95% of patients.<sup>191-193</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>194-197</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>198</sup> The results showed a response rate of 26% and an OS of 10.5 months.<sup>198</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

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cisplatin; or paclitaxel with carboplatin) as well as for other platinum-based chemotherapies currently used for urothelial carcinomas.<sup>193,199</sup> Oral targeted therapies generally do not produce responses in patients with renal medullary carcinoma. Outside of clinical trials, platinum-based chemotherapy regimens should be the preferred therapy for renal medullary carcinoma.

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

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

Imaging tests such as CT or MRI should be performed prior to initiating systemic treatment/observation; subsequent imaging may be performed every 6 to 16 weeks as per the physician's discretion and per the patient's clinical status. Imaging interval frequency should be altered according to rate of disease change and sites of active disease. The Panel recommends additional imaging such as CT or MRI of the head or spine, and bone scan at baseline and then as clinically indicated.

## **Supportive Care**

Supportive care remains a mainstay of therapy for all patients with metastatic RCC (<u>See NCCN Guidelines for Palliative Care</u>). 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>200</sup>

Surgery also may be appropriate for selected patients with malignant spinal cord compression, or impending or actual fractures in weightbearing 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>201-203</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>204,205</sup>

The role of bone-modifying agents such as bisphosphonates (eg, zoledronic acid) has been established in patients with various malignancies.<sup>206,207</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>208</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>208</sup>

The Panel recommends a bisphosphonate or a RANK ligand inhibitor for selected patients with bony metastases and creatinine clearance greater than or equal to 30 mL/min. Daily supplemental calcium and vitamin D are strongly recommended. Treatment for the palliation of symptoms,

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especially in patients with marginal performance status and evidence of metastatic disease, includes optimal pain management (See <u>NCCN</u> <u>Guidelines for Adult Cancer Pain</u>).

## Hereditary RCC Syndromes

While hereditary RCC is relatively rare (around 3% of all RCC cases),<sup>209</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, hereditary papillary renal carcinoma (HPRC), hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome, tuberous sclerosis complex (TSC), and VHL disease. The Guidelines describe kidney-specific clinical features and manifestations of each of these syndromes and known associated genes/inheritance patterns. They also provide genetic testing, surveillance, and treatment recommendations for patients 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 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 <u>NCCN Guidelines for Genetic/Familial</u> <u>High-Risk Assessment: Breast, Ovarian, and Pancreatic and NCCN</u> <u>Guidelines for Genetic/Familial High-Risk Assessment: Colorectal,</u> respectively. 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>10</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 patient'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 Patients with a Personal or Family History of an RCC Syndrome

The Panel recommends that patients with a personal or family history of an RCC syndrome who have not yet been diagnosed with RCC should undergo genetic evaluation. If patients harbor a pathogenic or likely pathogenic genetic mutation associated with an RCC syndrome, they should undergo screening for the development of RCC.

For screening in patients who are confirmed to have a hereditary RCC syndrome, the Panel recommends use of MRI (preferred). CT may also be used for surgical planning purposes, but the Panel warns that use of abdominal CT should be limited due to the potential of increased lifetime radiation exposure. The Panel also includes recommendations on testing intervals and the age at which patients should begin regular screening, as both vary widely by the hereditary RCC syndrome in question. While patients with HLRCC should undergo imaging annually,<sup>179</sup> those with less

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aggressive syndromes such as TSC may benefit from testing at longer intervals.<sup>210-212</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 should begin screening in childhood.<sup>179,210-213</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>210,214-216</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 pathological diagnosis of RCC and have characteristics potentially associated with a hereditary syndrome (eg, RCC diagnosis at ≤46 years of age, presence of bilateral or multifocal tumors, and/or ≥1 known first- or second-degree relative with RCC). These patients should also undergo genetic risk assessment, and if indicated, genetic testing. 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>217,218</sup> while patients with HLRCC should undergo total radical nephrectomy.<sup>179</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>219</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>218,220</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 (AMLs) not requiring immediate surgery.<sup>221,222</sup> The Panel included it as a category 2A, useful in certain circumstances recommendation for patients with TSC-associated AMLs.

The Panel also included erlotinib/bevacizumab for patients with HLRCCassociated metastatic RCC. While this regimen is not FDA-approved for use in this patient population, its inclusion is supported by clinical trial data showing improved patient outcomes. Erlotinib/bevacizumab treatment led to a 60% ORR and a median PFS of 24.2 months in 20 patients with HLRCC-associated RCC.<sup>223</sup> Based on these data, the Panel considers

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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>224</sup> Study-004, an open-label, phase II clinical trial, enrolled 61 patients with VHL-associated RCC; 77% had previously undergone surgery. Data were reported in a conference abstract.<sup>225</sup> The major efficacy endpoint was ORR, which was 49% (95% CI, 36-62). Median duration of response was not reached. Of the 30 patients who responded (all PRs), 17 patients (56%) had a duration of response of at least 12 months. Median time to response for patients with VHL-associated RCC tumors was 8 months.

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>226</sup>

## **Data Summary**

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

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

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Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	Median PFS (months)	Median OS (months)
Combination Therapy	,						
JAVELIN Renal 101 Choueiri et al 2020 <sup>116</sup> Motzer et al 2019 <sup>115</sup> Note: Only the most	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-1 1-positive	19	ORR: Overall population Axi/Ave: 53 (95% Cl, 48-57) Sunitinib: 27 (95% Cl, 23-32) ORR: PD-L1+ Axi/Ave: 56 (95% Cl, 50-62) Sunitinib: 27 (95% Cl, 22-33)	<u>Overall population</u> Axi/Ave: 13.3 (95% CI, 11.1-15.3) Sunitinib: 8.0 (95% CI, 6.7-9.8) HR, 0.69 (95% CI, 0.57-0.83) <i>P</i> < .0001 <u>PD-L1-positive</u>	$\frac{\text{Overall population}}{\text{Axi/Ave: Not estimable}}$ $(NE)$ $(95\% \text{ CI, 30-NE)}$ Sunitinib: NE $(95\% \text{ CI, 27.4-NE})$ HR, 0.80 $(95\% \text{ CI, 0.62-1.03})$ $P = .0392$ PD-L1-positive
recent data are shown.	Sunitinib	arm were P (PD Data from P 444 were report	(PD-L1+). Data from PD-L1+ patients were reported separately.		<u>CR (%): Overall</u> <u>population</u> Axi/Ave: 3.8 Sunitinib: 2.0 <u>CR (%): PD-L1+</u> Axi/Ave: 5.6 Sunitinib: 2.4	AXI/AVe: 13.8 (95% Cl, 10.1-20.7) Sunitinib: 7.0 (95% Cl, 5.7-9.6) HR, 0.62 (95% Cl, 0.49-0.78) <i>P</i> < .0001	Axi/Ave: NE (95% CI, NE-NE) Sunitinib: 28.6 (95% CI, 27.4-NE) HR, 0.83 (95% CI, 0.60-1.15) P = .1301
KEYNOTE-426	Axitinib + pembrolizumab	432	Favorable-, intermediate- or poor-risk, systemic therapy-	13	Axi/Pem: 59 (95% CI, 55-64) Sunitinib: 36	Axi/Pem: 15.1 (95% CI, 12.7-18.9) Sunitinib: 11.1 (95% CI, 9.1-12.5)	Axi/Pem: Not reached Sunitinib: Not reached
Rini et al 2019 <sup>™</sup>	Sunitinib	429	naïve, advanced ccRCC; Karnofsky PS ≥70%		(95% CI, 31-40) P < .001	HR, 0.69 (95% CI, 0.57-0.84) <i>P</i> < .001	HR, 0.53 (95% CI, 0.38-0.74) <i>P</i> < .0001
CheckMate 9ER Choueiri et al 2021 <sup>109</sup>	Cabozantinib + nivolumab	651	Favorable-, intermediate- or poor-risk, systemic therapy- naïve, advanced ccRCC; Karnofsky PS ≥70%		Cabo/Nivo: 56	Cabo/Nivo: 16.6 (95% CI, 12.5-14.9) Sunitinib: 8.3	Cabo/Nivo: Not reached (NR) Sunitinib: NR <u>12-month OS (%)</u> Cabo/Nivo: 86%
	Sunitinib	328		18	Sunitinib: 27 <i>P</i> < .001	HR, 0.51 (95% CI, 0.41-0.64) <i>P</i> < .001	(95% CI, 81–89) Sunitinib: 76% (95% CI, 71-80) HR, 0.60 (98.89% CI, 0.40-0.89) <i>P</i> = .001

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Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	Median PFS (months)	Median OS (months)
	lpilimumab + nivolumab	550	The study enrolled 425 intermediate-risk, 422 poor- risk, and 249 favorable-risk		<u>Intermediate-</u> <u>/poor-risk</u> <u>patients</u> <u>ORR</u> Ipi/Nivo: 42 (95% CI, 37-47) Sunitinib: 27 (95% CI, 22-31) <i>P</i> < .001	<u>Intermediate-/poor-</u> <u>risk patients</u> Ipi/Nivo: 11.6 (95% CI, 8.7-15.5) Sunitinib: 8.4 (95% CI, 7.0-10.8)	Intermediate-/poor-risk patients Ipi/Nivo: NR Sunitinib: 26 <u>18-month OS (%)</u> Ipi/Nivo: 75% (95% CI, 70-78) Sunitinib: 60% (95% CI, 55 65)
CheckMate 214 Motzer et al 2018 <sup>113</sup>	Sunitinib	546	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.	25	$\frac{CR (\%)}{Ipi/Nivo: 9}$ Sunitinib: 1 $P < .001$ $\frac{Favorable-risk}{Datients}$ $\frac{DRR}{Ipi/Nivo: 29}$ (95% CI, 21-38) Sunitinib: 52 (95% CI, 43-61) $P < .001$ $\frac{CR (\%)}{Ipi/Nivo: 11}$ Sunitinib: 6	HR, 0.82 (99.1% CI, 0.64-1.05) P = .03 (ns) <b>Favorable-risk</b> <b>patients</b> Ipi/Nivo: 15.3 (95% CI, 9.7-20.3) Sunitinib: 25.1 (95% CI, 20.9-NE) HR, 2.18 (99.1% CI, 1.29-3.68) P < .001	(95% CI, 55-65) HR, 0.63 (99.8% CI, 0.44-0.89) P < .001 <b>Favorable-risk patients</b> Ipi/Nivo: NR Sunitinib: 33 <u>18-month OS (%)</u> Ipi/Nivo: 88% (95% CI, 80-92) Sunitinib: 93% (95% CI, 87-97) HR, 1.45 (99.8% CI, 0.51-4.12) P = .27

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Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	Median PFS (months)	Median OS (months)
	Lenvatinib + pembrolizumab	355	355 357 Favorable-, intermediate- or poor-risk, systemic therapy- naïve, advanced ccRCC; Karnofsky PS ≥70% 357	27	<u>ORR</u> Len/Pem: 71 Len/Ev: 54 Sunitinib: 36	Len/Pem: 23.9 (95% Cl, 20.8-27.7) Len/Ev: 14.7 (95% Cl,11.1-16.7 ) Sunitinib: 9.2 (95% Cl, 6.0-11.0) $\frac{Len/Pem vs.}{Sunitinib}$ HR, 0.39 (95% Cl, 0.32-0.49) P < .001 $\frac{Len/Ev vs. Sunitinib}{HR, 0.65}$ (95% Cl, 0.53-0.80) P < .001	Len/Pem: NR Len/Ev: NR Sunitinib: NR Len/Pem vs. Sunitinib HR, 0.66 (95% Cl, 0.49-0.88) P = .005 Len/Ev vs. Sunitinib HR, 1.15 (95% Cl, 0.88-1.50) P = .30
CLEAR Motzer et al 2021 <sup>111</sup>	Lenvatinib + everolimus	357			ORR, Len/Pem vs. Sunitinib RR: 1.97 (95% Cl, 1.69-2.29) ORR, Len/Ev vs. Sunitinib RR: 1.48 (95% Cl, 1.26-1.74) CR Len/Pem: 16 Lev/Ev: 10 Sunitinib: 4		
	Sunitinib 357	357					
Monotherapy							
VEG105192 Sternberg et al 2013 <sup>118</sup> (OS data)	Pazopanib	290	Favorable-, intermediate-, or poor-risk, locally advanced or metastatic ccRCC; ECOG PS 0-1 Note: Of 435 enrolled	Median not reported; Up to 24 months for primary outcome	Pazopanib: 32 (95% Cl, 24-39) Placebo: 4 (95% Cl, 0-8)	Pazopanib: 11.1 Placebo: 2.8 HR, 0.40 (95% Cl, 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 not reported
Sternberg et al 2010 <sup>117</sup> (PFS and ORR data)	Placebo	145	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.				

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Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	Median PFS (months)	Median OS (months)
COMPARZ Motzer et al 2013 <sup>119</sup> Note: In 2014, updated OS data	Pazopanib	557	Favorable- or intermediate- risk, systemic therapy-naïve, advanced or metastatic ccRCC; Karnofsky PS ≥70%	Median not reported;	Descosile 24	Pazopanib: 8.4 (95% CI, 8.3-10.9) Sunitinib: 9.5	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
were reported in a correspondence letter to the publishing journal. <sup>120</sup> Only the most recent OS data are shown.	Sunitinib	553		Up to 48 months for primary outcome	Sunitinib: 25 P = .03	(95% CI, 0.3-11.1) HR, 1.05 (95% CI, 0.90-1.22) noninferior	
Phase III trial	Sunitinib	375	Favorable-, intermediate-, or poor-risk, systemic therapy- naïve, metastatic ccRCC; ECOG PS 0-1		Sunitinib: 31 (95% CI, 26-36)	Sunitinib: 11 (95% Cl, 10-12) Interferon: 5 (95% Cl, 4-6)	Sunitinib: NR Interferon: NR HR, 0.65 (95% CI, 0.45-0.94) P = .02 not significant
Motzer et al 2007 <sup>121</sup>	Interferon alfa	375		Not reported	Interferon: 6 (95% CI, 4-9) <i>P</i> < .001	HR, 0.42 (95% CI, 0.32-0.54) <i>P</i> < .001	

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

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Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)	
Combination Therapy								
Phase I/II study Apolo et al 2021 <sup>145</sup> (conference abstract)	Cabozantinib/nivolumab +/- ipilimumab	16	Favorable-, intermediate-, or poor-risk metastatic ccRCC; received at least one line of therapy; Karnofsky PS ≥70%	Not reported	Not reported	Not reported	38.6 (95% Cl, 19.4-NE)	
CheckMate 016 Hammers et al 2017 <sup>146</sup>	lpilimumab 1 mg/kg /nivolumab 3 mg/kg (N3l1)	47	Favorable-, intermediate-, or poor-risk advanced or metastatic ccRCC; received 0 to ≥4 lines of therapy; Karnofsky PS ≥80%		Treatment-	All treatment	All treatment settings:	
Hammers et al 2017 <sup>146</sup> Note: The study also included nivolumab/TKI and high-dose Ipi/Nivo arms, but these data were not reported.	lpilimumab 3 mg/kg /nivolumab 1 mg/kg (N1I3)	47	from treatment-experienced patients were reported separately; OS and PFS outcomes were combined. 22 patients in the N3I1 arm and 26 patients in the N1I3 arm were treatment- experienced.	22	experienced: N3I1: 46 N1I3: 39	Setunda. N311: 7.7 (95% Cl, 3.7-14.3) N113: 9.4 (95% Cl, 5.6-18.6)	N3I1: NR (95% CI, 26.7-NR) N1I3: 32.6 (95% CI, 26.0-NR)	

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Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
Phase II study Motzer et al 2016 <sup>140</sup> Motzer et al 2015 <sup>139</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	Len/Ev: 25.5 (95% Cl, 16.4-NE) Ev: 15.4 (95% Cl, 11.8-19.6) Len: 19.1
	Everolimus	50			Len/EV: 43 Ev: 6 Len: 27 <u>Len/Ev vs.</u> <u>Len</u> <i>P</i> < .0001 <u>Len vs. Ev</u> <i>P</i> = .0067	(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 <u>Len/Ev vs. Len</u> HR, 0.66	(95% Cl, 13.6-26.2) <u>Len/Ev vs. Ev</u> HR, 0.51 (95% Cl, 0.30-0.88) <i>P</i> = .024 <u>Len vs. Len/Ev</u> HR, 0.75
	Lenvatinib	52				(95% CI, 0.39-1.10) <i>P</i> = .12 <u>Len vs. Ev</u> HR, 0.61 (95% CI, 0.39-0.98) <i>P</i> = .048	(95% Cl, 0.43-1.30) <i>P</i> = .32 <u>Len vs. Ev</u> HR, 0.68 (95% Cl, 0.41-1.14) <i>P</i> = .12
KEYNOTE-146 Lee et al 2021 <sup>147</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	<u>Week 24</u> 2+L, ICI- naïve: 41 2+L, ICI-TE: 56 TN: 73 <u>Overall</u> 2+L, ICI- naïve: 63 2+L, ICI-TE: 53 TN: 77	2+L, ICI-naïve: 11.8 (95% CI, 5.5-21.9) 2+L, ICI-TE: 12.2 (95% CI, 9.5-17.7) TN: 24.1 (95% CI, 11.7-31.7)	2+L, ICI-naïve: 30.3 (95% CI, 28.7-NR) 2+L, ICI-TE: NR (95% CI, NR-NR) TN: NR (95% CI, 28.6-NR)
	Lenvatinib/pembrolizumab, ICI treatment-experienced (2+L ICI-TE)	104					
	Lenvatinib/pembrolizumab, treatment-naïve (TN)	22					

## **NCCN Guidelines Version 3.2022** NCCN Comprehensive Cancer Network® **Kidney Cancer**

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
Monotherapy							
AXIS Motzer et al 2013 <sup>143</sup> Rini et al 2011 <sup>127</sup>	Axitinib	361	Favorable-, intermediate-, or poor-risk, systemic therapy-	Up to 36	Axi: 19 Sor: 9 P = .0001	Axi: 8.3 (95% CI, 6.7-9.2) Sor: 5.7 (95% CI, 4.7-6.5)	Axi: 20.1 (95% Cl, 16.7-23.4) Sor: 19.2 (95% Cl, 17.5-22.3)
Note: Only the most recent data are shown.	Sorafenib	362	naïve metastatic ccRCC; ECOG PS 0-1	months		HR, 0.67 (95% CI, 0.55-0.78) <i>P</i> < .0001	HR, 0.97 (95% CI, 0.80-1.17) P = .37
METEOR Motzer et al 2018 <sup>135</sup> Choueiri et al 2016 <sup>134</sup>	Cabozantinib	330	Favorable-, intermediate-, or poor-risk advanced or metastatic ccRCC; received	OS: 22 <sup>135</sup>	Cabo: 17	Cabo: 7.4 (95% Cl, 6.6-9.1) Ev: 3.9 (95% Cl, 3.7-5.1)	Cabo: 21.4 Ev: 17.1
Choueiri et al 2015 <sup>133</sup> Note: Only the most recent outcome data are shown.	Everolimus	328	TKI with progression within 6 months of treatment; Karnofsky PS ≥70%	ORR, PFS: 19 <sup>134</sup>	EV: 3 P < .0001	HR, 0.51 (95% CI, 0.41-0.62) <i>P</i> < .0001	HR, 0.70 (95% Cl, 0.58-0.85) <i>P</i> = .0002
CheckMate 025	Nivolumab	406	Favorable-, intermediate-, or poor-risk advanced or metastatic ccRCC; received 1-2 prior antiangiogenic	Minimum 14	Nivo: 25 Ev: 5 P < .001	Nivo: 4.6 (95% CI, 3.7-5.4) Ev: 4.4 (95% CI, 3.7-5.5)	Nivo: 25.0 (95% CI, 21.8-NE) Ev: 19.6 (95% CI, 17.6-23.1)
Motzer et al 2015 <sup>141</sup>	Everolimus	397	<ul> <li>1-2 prior antiangiogenic therapies (except mTOR inhibitors); Karnofsky PS ≥70%</li> </ul>			HR, 0.88 (95% CI, 0.75-1.03) <i>P</i> = .11	HR, 0.73 (95% Cl, 0.57-0.93) <i>P</i> = .002
VEG105192 Sternberg et al 2013118 (OS data)Pazopanib290Sternberg et al 2010117 (PFS and ORR data)Placebo145	290	Favorable-, intermediate-, or poor-risk locally advanced or metastatic ccRCC; ECOG PS 0-1	Median not reported; Up to 24		Paz: 7.4 Placebo: 4.2	Paz: 23 Placebo: 19	
	Placebo	145	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.	months for primary outcome	Placebo: 3	HR, 0.54 (95% CI, 0.35-0.84) <i>P</i> < .001	HR, 0.82 (95% CI, 0.57-1.16) <i>P</i> value not reported

## **NCCN Guidelines Version 3.2022** Comprehensive **Kidney Cancer**

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
	Tivozanib	175	Favorable-, intermediate-, or poor-risk metastatic ccRCC;			Tivo: 5.6 (95% CI, 5.3-7.3) Sor: 3.9	Tivo: 16.4 (95% CI, 13.4-22.2) Sor: 19.7
TIVO-3 Rini et al 2020 <sup>156</sup> Sorafenib	175	therapies including at least 1 VEGFR-targeted TKI other than sorafenib or tivozanib; ECOG PS 0-1	19	Tivo: 18 Sor: 8	(95% CI, 3.7-5.6) HR, 0.73 (95% CI, 0.56-0.94) <i>P</i> = .016	(95% Cl, 15.0-24.2) HR, 0.99 (95% Cl, 0.76-1.29) <i>P</i> = .95	

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

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Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)	
Combination Therapy								
Phase II trial Hutson et al 2021 <sup>173</sup>	Lenvatinib/everolimus	31	Unresectable advanced or metastatic nccRCC	Not reported	26	9.2 (95% CI, 5.5-NE)	15.6 (95% CI, 9.2-NE)	
Monotherapy								
Phase II SWOG 1500 trial Pal et al 2021 <sup>169</sup>	Cabozantinib	46	Favorable-, intermediate-, or poor-risk metastatic papillary	Not reported; up to 36	Cabo: 23	Cabo: 9.0 (95% CI, 6-12) Sun: 5.6 (95% CI, 3-7)	Cabo: 20.0 Sun: 16.4	
Note: The trial also included savolitinib and crizotinib groups; assignment was halted after a futility analysis.	Sunitinib	44	RCC; previously received 0- 1 therapies, excluding VEGFR and MET TKIs	months followup specified in trial	Sun: 4 P = .010	HR, 0.60 (95% CI, 0.37- 0.97) <i>P</i> = .019	HR, 0.84 (95% CI, 0.47-1.51) Not significant	
Retrospective study Koshkin et al 2018 <sup>174</sup>	Nivolumab	35	Metastatic nccRCC	9	PR: 20 SD: 29	3.5	Not reported	

## **NCCN Guidelines Version 3.2022** NCCN Comprehensive Cancer Network® **Kidney Cancer**

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
Phase II KEYNOTE-427 (cohort B) McDermott et al 2021 <sup>176</sup>	Pembrolizumab	165	Favorable-, intermediate-, or poor-risk, systemic therapy- naïve, newly diagnosed or recurrent stage IV nccRCC; Karnofsky PS ≥70%	32	27	4.2 (95% Cl, 2.9-5.6)	28.9 (95% Cl, 24.3-NE)
Phase II ASPEN trial	Sunitinib	51	Favorable-, intermediate-, or poor-risk, systemic therapy-		Sun: 18 Evero: 9	Sun: 8.3 (80% Cl, 5.8-11.4) Evero: 5.6 (80% Cl, 5.5-6.0)	Sun: 31.5 (95% Cl, 14.8-NE) Evero: 13.2 (95% Cl, 9,7-37.9)
Armstrong et al 2016 <sup>170</sup> Everolimus	Everolimus	57	(papillary, chromophobe, or unclassified); Karnofsky PS ≥60%	12-13		HR, 1.41 (80% CI, 1.03- 1.92) <i>P</i> = .16	HR, 1.12 (95% Cl, 0.7-2.1) P = .60
Phase II ESPN trial	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			Sun: 6.1 (95% CI, 4.2-9.4)	Sun: 16.2 (95% CI, 14.2-NE) Evero: 14.9 (95% CI, 8.0-23.4) <i>P</i> = .18
Phase II ESPN trial Tannir et al 2016 <sup>171</sup>	Everolimus	35		24	6	Evero: 4.1 (95% CI, 2.7-10.5) <i>P</i> = .60	

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