National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Kidney Cancer

Version 3.2024 — March 11, 2024

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¥ Patient advocacy
≠ Pathology
§ Radiotherapy/Radiation oncology
ω Urology
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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 3.2024 of the NCCN Guidelines for Kidney Cancer from Version 2.2024 include:

KID-3

- Relapse or Stage IV
  - Footnote h, last sentence added: An FDA-approved biosimilar is an appropriate substitute for denosumab.

Updates in Version 2.2024 of the NCCN Guidelines for Kidney Cancer from Version 1.2024 include:

KID-C (2 of 3)

- Subsequent Therapy for Clear Cell Histology
  - Prior IO Therapy, Useful in Certain Circumstances
    - ◊ Belzutifan changed from a category 2B to a category 2A recommendation and moved to Other Recommended Regimens.
- Footnote f added: This regimen is for patients that have received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

Updates in Version 1.2024 of the NCCN Guidelines for Kidney Cancer from Version 4.2023 include:

KID-1

- Initial workup
  - Stage I (T1b)
    - ◊ Option added: Ablative techniques (in select patients)
- Footnote removed: If metastatic disease is present or the patient cannot tolerate ureteroscopy.

KID-A

- Title revised: *General* Principles of *Management for Renal Cell Carcinoma* ~~Surgery~~
  - Bullet 6 revised: Thermal ablation (eg, cryosurgery, radiofrequency ablation*, microwave ablation*) is an option for the management of ~~patients with~~ clinical stage T1 renal lesions.
  - Bullet 6, sub-bullet removed: Thermal ablation is an option for masses <3 cm, but may also be an option for larger masses in select patients. Ablation in masses >3 cm is associated with higher rates of local recurrence/persistence and complications.
  - Bullet 6, sub-bullet 1 added: Thermal ablation is an option for clinical T1b masses in select patients not eligible for surgery.
  - Bullet 6, sub-bullet 2 revised: *Biopsy of lesions is recommended to be done prior to or at time of ablation.* ~~Biopsy of small lesions confirms a diagnosis of malignancy for surveillance, cryosurgery, and radiofrequency ablation strategies.~~
  - Bullet 7 added: SBRT is considered an ablative therapy and may be considered for medically inoperable patients (not optimal surgical candidates) with stage I (category 2B), II, or III (both category 3) kidney cancer.
  - Bullet 8, sub-bullet 1 revised: Small renal masses <*3*~~2~~ cm given the high rates of benign tumors and low metastatic potential of these masses.
  - Bullet 10 added: Patients either with large-volume distant metastases or tumors with large sarcomatoid burdens should receive systemic therapy prior to cytoreductive nephrectomy

KID-B (1 of 5)

- Follow-up
  - Header revised: Stage 1 ~~(T1a)~~
    - ◊ Follow-up During Active Surveillance
      - – Bullet 3, sub-bullet revised: Abdominal CT or MRI with *and without IV* contrast if no contraindication within 6 months of surveillance initiation, then CT, MRI, or ultrasound (US) at least annually
    - ◊ Follow-up After Ablative Techniques
      - – Bullet 3, sub-bullet 1 revised: Abdominal CT*,* ~~or~~ MRI with and without IV contrast (unless otherwise contraindicated)*, or contrast-enhanced US at 1–3 months, 6 months, and 12 months after ablation, then annually thereafter.* ~~at 1–6 mo following ablative therapy, then CT or MRI (preferred) annually for 5 y or longer as clinically indicated.~~ If patient is unable to receive IV contrast, MRI *or contrast-enhanced US are* ~~is~~ the preferred imaging modalit*iesy*
      - – Bullet 3, sub-bullet 2 revised: If there is imaging or clinical concern~~s~~ for *residual or recurrent disease* ~~recurrence~~, then ~~more frequent imaging,~~ renal mass biopsy~~,~~ or further treatment may be indicated
- Footnote c revised: *CT is with IV contrast and MRI is with or without contrast.* ~~Imaging with contrast when clinically indicated.~~ (Also for KID-B 2 and 4)

UPDATES

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Kidney Cancer from Version 4.2023 include:

KID-B (3 of 5)
- Footnote c added: CT is with IV contrast and MRI is without or with contrast.

KID-C (3 of 3)
- Systemic Therapy for Non-Clear Cell Histology
  - Preferred regimens
    - Sunitinib was moved to Other Recommended Regimens.

HERED-RCC-1
- Criteria for Further Genetic Risk Evaluation for Hereditary RCC Syndromes
  - Criteria 4, bullet 2 revised: Any first-degree relative who meets the criteria in boxes 2 ~~and~~ *or* 3 who is unable or unwilling to genetically test
- Footnotes
  - Footnote c added: Using age as a sole criterion for genetic risk evaluation is generally not a sensitive method.

HERED-RCC-2
- Hereditary RCC Syndromes Overview
  - Column 2, row 2 revised: ~~Type 1~~ Papillary
  - Column 2, row 3 revised: Chromophobe, hybrid oncocytic tumors, *clear cell, oncocytomas, angiomyolipomas,* papillary RCC
  - Column 2, row 4 revised: Angiomyolipoma *(and other PEComas)*, *renal cysts, eosinophilic solid and cystic RCC, RCC with fibromyomatous stroma, eosinophilic vacuolated tumor, low-grade oncocytic tumor,* clear cell
  - Column 2, row 5 revised: HLRCC *associated RCC* or FH-*deficient* ~~associated~~ RCC~~/type 2 papillary~~
  - Column 2, row 6 revised: Clear cell~~, chromophobe~~
  - Column 2, row 7 revised: *SDH deficient RCC* ~~Clear cell (not usually SDHB), chromophobe, papillary type 2, renal oncocytoma, oncocytic neoplasm~~

GENE-1
- Column 1 revised: *Individuals with* syndrome features *(HERED-RCC-2)*/*or* criteria in HERED-RCC-1 met

HERED-RCC-A
- Table 2: Features of Von Hippel-Lindau (VHL) Disease
  - Major Features
    - Bullet 3 revised: Pheochromocytoma (PCCs)

HERED-RCC-B (2 of 2)
- Reference 9 added: Binderup MLM, Smerdel M, Borgwadt L, et al. von Hippel-Lindau disease: Updated guideline for diagnosis and surveillance. Eur J Med Genet 2022;65:104538.

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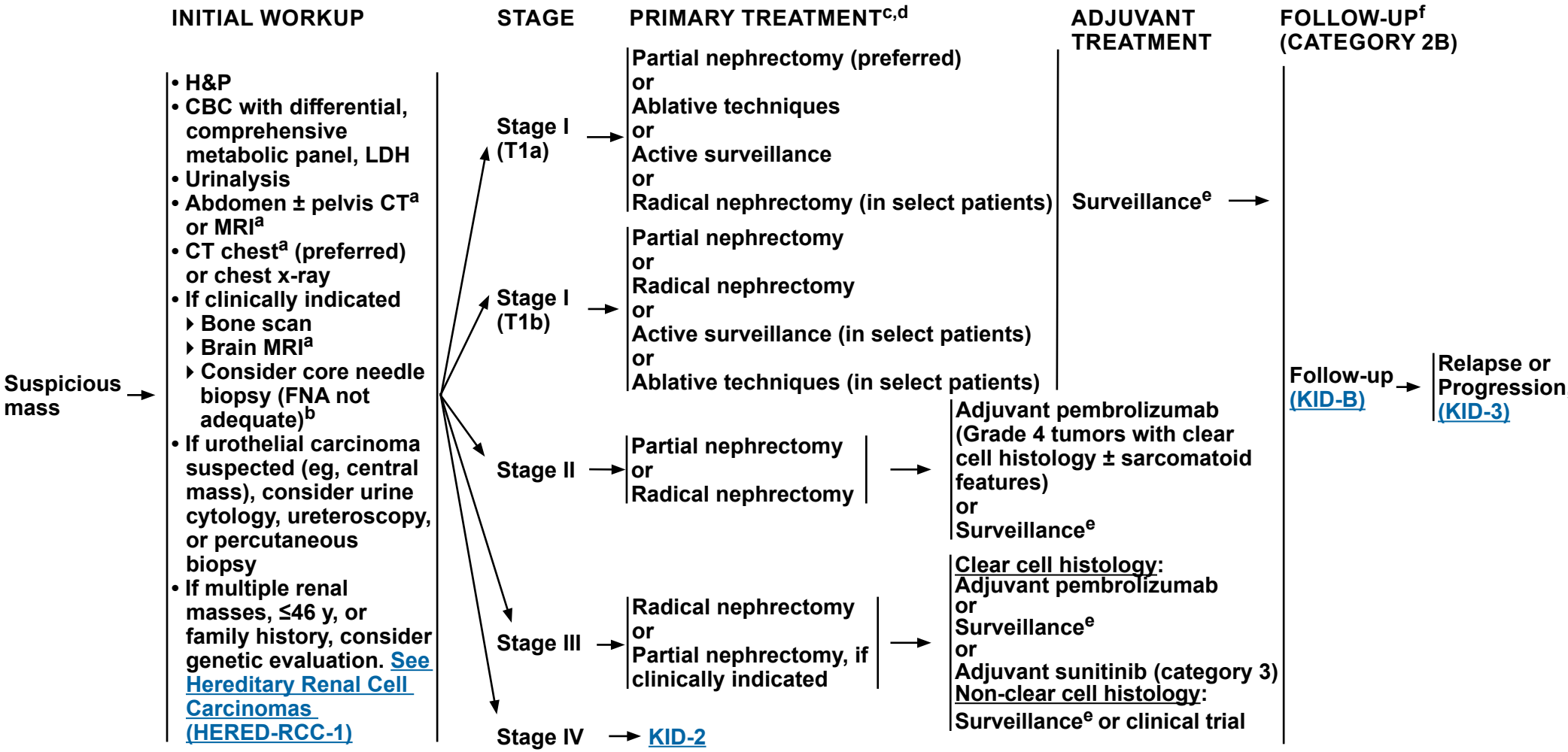
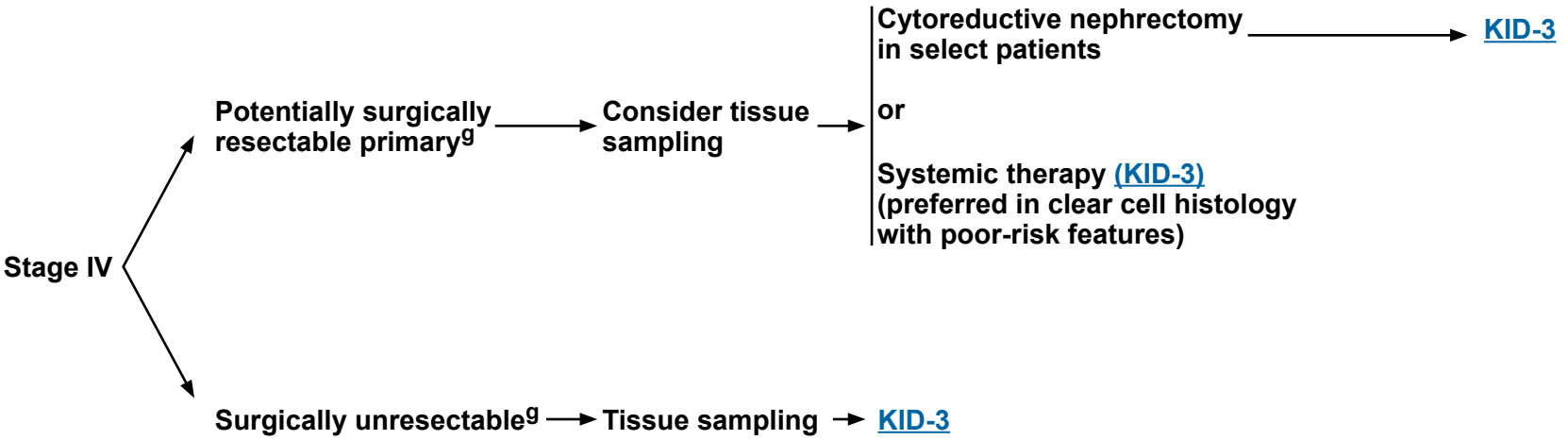


[a] Imaging with and without contrast is strongly preferred, such as a renal protocol.
[b] Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance or ablative techniques, cryosurgery, and radiofrequency ablation strategies.
[c] Principles of Surgery (KID-A).
[d] Stereotactic body radiation therapy (SBRT) may be considered for medically inoperable patients with stage I kidney cancer (category 2B) or with stage II/III kidney cancer (both category 3).
[e] Follow-up (KID-B).
[f] No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

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



[c] Principles of Surgery (KID-A).
[g] Individualize treatment based on symptoms and extent of metastatic disease.

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RELAPSE OR STAGE IV

	TREATMENT	DISEASE PROGRESSION
Clear cell histology →	Clinical trial or First-Line Therapy (KID-C, 1 of 3) or Metastasectomy or stereotactic body radiation therapy (SBRT) or ablative techniques for oligometastatic disease or Metastasectomy with complete resection of disease, followed by adjuvant pembrolizumab within 1 year of nephrectomy and Best supportive care[h] → Follow-up (KID-B)	→ Clinical trial or Subsequent Therapy for Clear Cell Histology (KID-C, 2 of 3) and Best supportive care[h] or Metastasectomy or SBRT or ablative techniques for oligometastatic disease
Non-clear cell histology →	Clinical trial (preferred) or Systemic Therapy (KID-C, 3 of 3) or Metastasectomy or SBRT or ablative techniques for oligometastatic disease and Best supportive care[h] → Follow-up (KID-B)	→ Clinical trial or Systemic Therapy for Non-Clear Cell Histology (KID-C, 3 of 3) and Best supportive care[h] or Metastasectomy or SBRT or ablative techniques for oligometastatic disease

[h] Best supportive care can include palliative radiation therapy (RT), bisphosphonates, or receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors for bony metastases. An FDA-approved biosimilar is an appropriate substitute for denosumab.

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GENERAL PRINCIPLES OF MANAGEMENT FOR RENAL CELL CARCINOMA

- **Nephron-sparing surgery (partial nephrectomy) is recommended in select patients, such as:**
  - **Unilateral stage I–III tumors where technically feasible**
  - **Uninephric state, renal insufficiency, bilateral renal masses, and familial renal cell cancer**
  - **Patients at relative risk for developing progressive chronic kidney disease due to young age or medical risk factors (ie, hypertension, diabetes, nephrolithiasis)**

- **Open, laparoscopic, or robotic surgical techniques may be used to perform radical and partial nephrectomies.**

- **Regional lymph node dissection is optional but should be considered for patients with resectable adenopathy on preoperative imaging or palpable/visible adenopathy at time of surgery.**

- **If adrenal gland is uninvolved, adrenalectomy may be omitted.**

- **Special teams or referral to high-volume centers may be required for extensive inferior vena cava involvement.**

- **Thermal ablation (eg, cryosurgery, radiofrequency ablation, microwave ablation) is an option for the management of clinical stage T1 renal lesions.**
  - **Thermal ablation is an option for clinical T1b masses in select patients not eligible for surgery.**
  - **Biopsy of lesions is recommended to be done prior to or at time of ablation.**
  - **Ablative techniques may require multiple treatments to achieve the same local oncologic outcomes as conventional surgery.[a,b]**

- **SBRT is considered an ablative therapy and may be considered for medically inoperable patients (not optimal surgical candidates) with stage I (category 2B), II, or III (both category 3) kidney cancer (KID-1).**

- **Active surveillance is an option for the initial management of patients with clinical stage T1 renal lesions, for example:**
  - **Small renal masses <3 cm given the high rates of benign tumors and low metastatic potential of these masses.**
  - **Active surveillance of patients with T1a tumors (≤4 cm) that have a predominantly cystic component is recommended.**
  - **Patients with clinical stage T1 masses and significant competing risks of death or morbidity from intervention.**
  - **Active surveillance entails serial abdominal imaging with timely intervention should the mass demonstrate changes (eg, increasing tumor size, growth rate, infiltrative pattern) indicative of increasing metastatic potential.**
  - **Active surveillance should include periodic metastatic survey including blood work and chest imaging, particularly if the mass demonstrates growth.**

- **Generally, patients who would be candidates for cytoreductive nephrectomy prior to systemic therapy have:**
  - **Excellent performance status (ECOG PS <2)**
  - **No brain metastasis**

- **Patients either with large-volume distant metastases or tumors with large sarcomatoid burdens should receive systemic therapy prior to cytoreductive nephrectomy.**

[a] Campbell S, Uzzo R, Allaf M, et al. Renal mass and localized renal cancer: AUA Guideline. J Urol 2017;198:520-529.
[b] Pierorazio P, Johnson M, Patel H, et al. Management of renal masses and localized renal cancer: Systematic review and meta-analysis. J Urol 2016;196:989-999.

Note: All recommendations are category 2A unless otherwise indicated.
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FOLLOW-UP[a,b] (category 2B)

Stage I

Follow-up During Active Surveillance[c]

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

Follow-up After Ablative Techniques[c]

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

[a] Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.
[b] No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years (KID-B, 5 of 5). Further study is required to define optimal follow-up duration.
[c] CT is with IV contrast and MRI is with or without contrast.

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FOLLOW-UP[a,b,c] (category 2B)

Stage I

Follow-up After a Partial or Radical Nephrectomy

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

Stage II

Follow-up After a Partial or Radical Nephrectomy

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

[a] Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.
[b] No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years (KID-B, 5 of 5). Further study is required to define optimal follow-up duration.
[c] CT is with IV contrast and MRI is with or without contrast.

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FOLLOW-UP[a,b,c]
(category 2B)

Follow-up for Stage III

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

[a] Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.
[b] No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years (KID-B, 5 of 5). Further study is required to define optimal follow-up duration.
[c] CT is with IV contrast and MRI is with or without contrast.

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FOLLOW-UP
(category 2B)

Follow-up After Adjuvant Therapy

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

Follow-up for Relapsed or Stage IV and Surgically Unresectable Disease[c,d]

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

[c] CT is with IV contrast and MRI is with or without contrast.
[d] No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on treatment schedules, side effects, comorbidities, and symptoms.

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FOLLOW-UP
(category 2B)

Long-Term Follow-Up (>5 years)

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

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

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

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

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

Ablation

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

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

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

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

Locally Advanced Disease

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

Long-Term Follow-Up

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

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

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

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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1)	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Ipilimumab + nivolumab[b] • Pazopanib • Sunitinib	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d] (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[d] (category 3) • Temsirolimus[e] (category 3)

[a] Risk Models to Direct Treatment (IMDC criteria or MSKCC Prognostic Model) (KID-D).
[b] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[c] Rini BI, et al. Lancet Oncol 2016;17:1317-1324. Harrison MR, et al. Cancer 2021;127:2204-2212. Bex A. Cancer 2021;127:2184-2186.
[d] Patients with excellent performance status and normal organ function.
[e] The poor risk model used in the global advanced renal cell carcinoma (ARCC) trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin less than the lower limit of normal (LLN), corrected calcium >10 mg/dL, LDH >1.5 times the upper limit of normal (ULN), and metastasis in multiple organs. Hudes G, et al. N Engl J Med 2007;356:2271-2281.

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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)

Immuno-oncology (IO) Therapy History Status	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
IO Therapy Naïve	• None	• Axitinib + pembrolizumab[b] • Cabozantinib • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + everolimus • Lenvatinib + pembrolizumab[b] • Nivolumab[b]	• Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib[g] • Belzutifan (category 2B) • Bevacizumab[h] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)
Prior IO Therapy	• None	• Axitinib • Belzutifan[f] • Cabozantinib • Lenvatinib + everolimus • Tivozanib[g]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Everolimus • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Bevacizumab[h] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)

[b] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[d] Patients with excellent performance status and normal organ function.
[e] The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium >10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, et al. N Engl J Med 2007;356:2271-2281.
[f] This regimen is for patients that have received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).
[g] For patients who received ≥2 prior systemic therapies.
[h] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

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

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[i]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Clinical trial • Cabozantinib	• Lenvatinib + everolimus • Nivolumab[b] • Nivolumab[b] + cabozantinib • Pembrolizumab[b] • Sunitinib	• Axitinib • Bevacizumab[h] • Bevacizumab[h] + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated RCC (HERED-RCC-D) • Bevacizumab[h] + everolimus • Erlotinib • Everolimus • Nivolumab[b] + ipilimumab[b] (category 2B) • Pazopanib • Temsirolimus[e] (category 1 for poor-prognosis risk group; category 2A for other risk groups)

[b] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

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

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

[i] For collecting duct or medullary subtypes, partial responses have been observed with cytotoxic chemotherapy (carboplatin + gemcitabine, carboplatin + paclitaxel, or cisplatin + gemcitabine) and other platinum-based chemotherapies currently used for urothelial carcinomas. Gemcitabine + doxorubicin can also produce responses in renal medullary carcinoma (RMC) (Wilson NR, et al. Clin Genitourin Cancer 2021;19:e401-e408). Oral targeted therapies generally do not produce responses in patients with RMC; erlotinib + bevacizumab can produce responses even in heavily pretreated patients with RMC. Outside of clinical trials, platinum-based chemotherapy regimens should be the preferred first-line therapy for RMC.

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

RISK MODELS TO DIRECT TREATMENT

Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model[a]

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

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

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

Prognostic Factors
- Less than one year from time of diagnosis to systemic therapy
- Performance status <80% (Karnofsky)
- Hemoglobin < lower limit of normal (Normal: 120 g/L or 12 g/dL)
- Calcium > upper limit of normal (Normal: 8.5–10.2 mg/dL)
- Neutrophil > upper limit of normal (Normal: 2.0–7.0×10^9/L)
- Platelets > upper limit of normal (Normal: 150,000–400,000)

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

[a] Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 2002;20:289-296.
[b] Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. J Clin Oncol 2009;27:5794-5799.

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CRITERIA FOR FURTHER GENETIC RISK EVALUATION FOR HEREDITARY RCC SYNDROMES[a]

1. An individual with a close blood relative[b] with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene	→ GENE-1
2. An individual with RCC with any of the following criteria: ▸ Diagnosed at age ≤46 y[c] ▸ Bilateral or multifocal tumors ▸ ≥1 first- or second-degree relative[b] with RCC	→ Consider referral to cancer genetics professional and Refer to specific syndromes - See Hereditary RCC Syndromes Overview (HERED-RCC-2), See NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic: Principles of Cancer Risk Assessment and Counseling (EVAL-A) and Pedigree (EVAL-B) → GENE-1
3. An individual whose tumors have the following histologic characteristics: ▸ Multifocal papillary histology ▸ HLRCC-associated RCC, RCC with fumarate hydratase (FH) deficiency or other histologic features associated with HLRCC ▸ Birt-Hogg-Dubé syndrome (BHDS)-related histology (multiple chromophobe, oncocytoma, or oncocytic hybrid) ▸ Angiomyolipomas of the kidney and one additional tuberous sclerosis complex (TSC) criterion in the same person (Table 1) ▸ Succinate dehydrogenase (SDH)-deficient RCC histology[d]	→
4. An unaffected individual[e,f] with any of the following criteria: ▸ ≥2 first- or second-degree relatives[b] with RCC (on the same side of the family) ▸ Any first-degree relative who meets the criteria in boxes 2 or 3 who is unable or unwilling to genetically test	→

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

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

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

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

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

[f] Unnecessary in translocational RCC or medullary RCC.

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

HEREDITARY RCC SYNDROMES OVERVIEW

Syndrome/Gene	Common Histologies	Inheritance Pattern Major Clinical Manifestations	Other Specialists Involved in Screening
von Hippel-Lindau (VHL)/ *VHL* gene	Clear cell	• Autosomal dominant • Table 2	• Neurosurgery • Ophthalmology • Audiology • Endocrinology • Endocrine surgery
Hereditary papillary renal carcinoma (HPRC)/*MET* gene	Papillary	• Autosomal dominant • Multifocal, bilateral renal cell tumors	• Nephrology
Birt-Hogg-Dubé syndrome (BHDS)/*FLCN* gene[1,2]	Chromophobe, hybrid oncocytic tumors, clear cell, oncocytomas, angiomyolipomas, papillary RCC	• Autosomal dominant • Cutaneous fibrofolliculoma or trichodiscoma, pulmonary cysts, and spontaneous pneumothorax	• Pulmonology • Dermatology
Tuberous sclerosis complex (TSC)/*TSC1, TSC2* genes	Angiomyolipoma (and other PEComas), renal cysts, eosinophilic solid and cystic RCC, RCC with fibromyomatous stroma, eosinophilic vacuolated tumor, low-grade oncocytic tumor, clear cell	• Autosomal dominant • Table 1	• Neurology • Dermatology
Hereditary leiomyomatosis and renal cell cancer (HLRCC)/*FH* gene	HLRCC associated RCC or FH-deficient RCC	• Autosomal dominant • Leiomyomas of skin and uterus, unilateral, solitary, and aggressive renal cell tumors. PET-positive adrenal adenomas	• Gynecology • Dermatology
BAP1 tumor predisposition syndrome (TPDS)/*BAP1* gene[3,4]	Clear cell	• Autosomal dominant • Melanoma (uveal and cutaneous), kidney cancer, mesothelioma	• Dermatology • Ophthalmology • Thoracic oncology
Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome/*SDHA/ B/C/D* genes	SDH-deficient RCC	• Autosomal dominant • Head and neck PGL and adrenal or extra-adrenal PCCs, gastrointestinal stromal tumors (GIST)	• Endocrine • Endocrine surgery

[1] Schmidt LS, Nickerson ML, Warren MB, et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dubé syndrome. Am J Hum Genet 2005;76:1023-1033.
[2] Sattler EC, Steinlein OK. Birt-Hogg-Dubé Syndrome. 2006 Feb 27 [Updated 2020 Jan 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle;1993-2020.
[3] Peña-Llopis S, Vega-Ruweather bín-de-Celis S, Liao A. BAP1 loss defines a new class of renal cell carcinoma. Nat Genet 2012;44:751-759.
[4] Hakimi AA, Ostrovnaya I, Reva B. Adverse outcomes in clear cell renal cell carcinoma with mutations of 3p21 epigenetic regulators BAP1 and SETD2: a report by MSKCC and the KIRC TCGA Research Network. Clin Cancer Res 2013;19:3259-3267.

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See GENE-1

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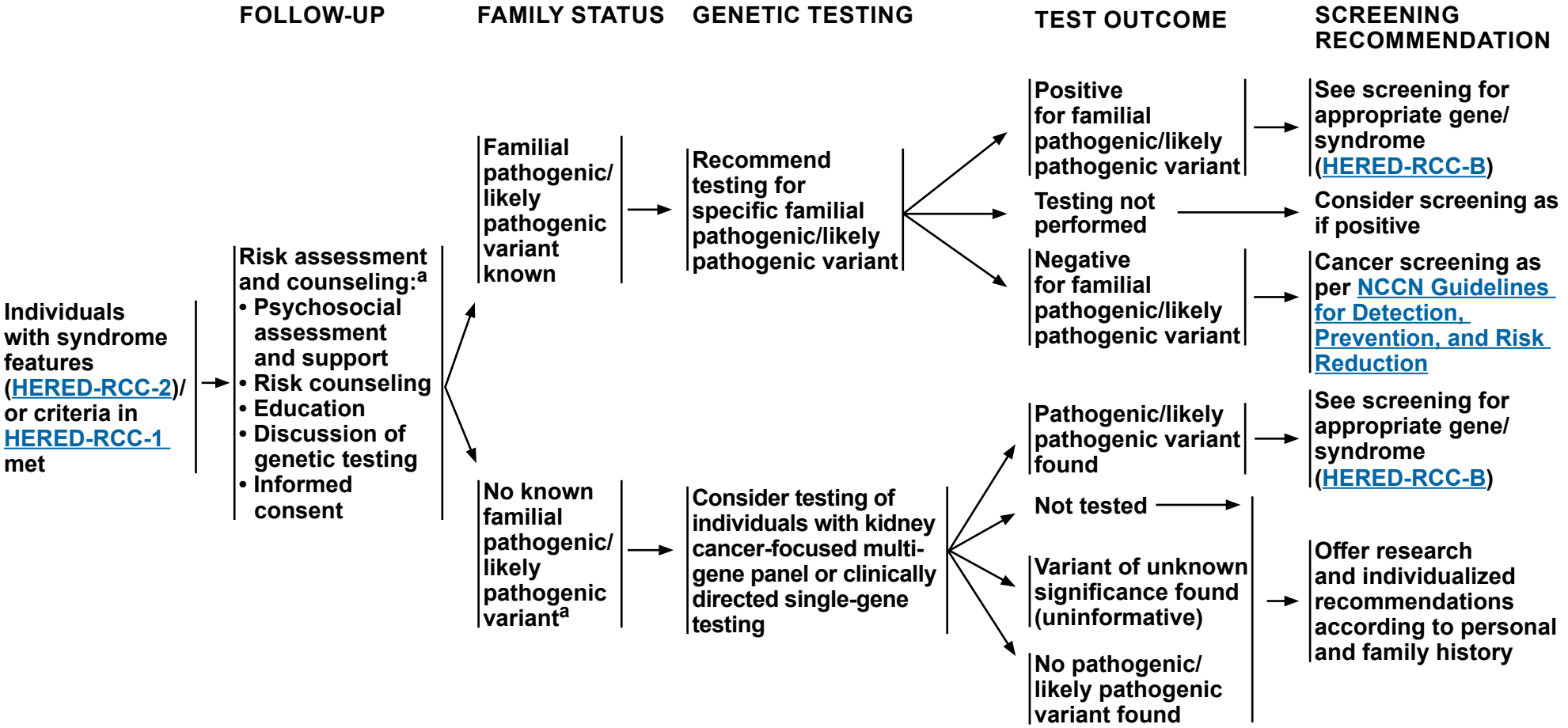

[a] In individuals who meet diagnostic criteria, but in whom no germline mutations are identified, consider workup for mosaicism.

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

Table 1: Features of Tuberous Sclerosis (TSC)

Major Features	Minor Features
• Renal angiomyolipoma[a,b] • Cardiac rhabdomyoma • Cortical dysplasias, including tubers and cerebral white matter migration lines • Angiofibromas (≥3) or fibrous cephalic plaque • Hypomelanotic macules (3 to >5 mm in diameter) • Lymphangioleiomyomatosis (LAM)[a] • Multiple retinal nodular hamartomas • Shagreen patch • Subependymal giant cell astrocytoma (SEGA) • Subependymal nodules (SENs) • Ungual fibromas (≥2)	• Multiple renal cysts • "Confetti" skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs) • Dental enamel pits (>3) • Intraoral fibromas (≥2) • Nonrenal hamartomas • Retinal achromic patch

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

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

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

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

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

General

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

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

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

References on HERED-RCC-B 2 of 2

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

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

KIDNEY-SPECIFIC SURGICAL RECOMMENDATIONS FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

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

***BAP1*-TPDS**
- **There are no specific guidelines in surgical management for this syndrome (KID-A).**

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

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

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

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

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

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

References on HERED-RCC-C 2 of 2

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

KIDNEY-SPECIFIC SURGICAL RECOMMENDATIONS FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

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[1] Pavlovich CP, Grubb RL 3rd, Hurley K, et al. Evaluation and management of renal tumors in the Birt-Hogg-Dubé syndrome. J Urol 2005;173:1482-1486.
[2] Menko FH, Maher ER, Schmidt LS, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. Fam Cancer 2014;13:637-644.
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[4] Krueger DA, Northrup H; International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013;49:255-265.
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[8] Singer EA, Vourganti S, Lin KY, et al. Outcomes of patients with surgically treated bilateral renal masses and a minimum of 10 years of followup. J Urol 2012;188:2084-2088.

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

KIDNEY-SPECIFIC SYSTEMIC THERAPY FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

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

[a] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[b] There are no specific FDA-approved therapies for HLRCC. Treatment with erlotinib plus bevacizumab demonstrated benefit in patients with metastatic RCC from HLRCC. Srinivasan R, Gurram S, Al Harthy M, et al. Results from a phase II study of bevacizumab and erlotinib in subjects with advanced hereditary leiomyomatosis and renal cell cancer (HLRCC) or sporadic papillary renal cell cancer [abstract]. J Clin Oncol 2020;38:(15_suppl) 5004-5004.
[c] Everolimus is an FDA-approved therapy for asymptomatic, growing angiomyolipoma measuring >3 cm in diameter. Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2013;381:817-824.
[d] Belzutifan is FDA-approved for the treatment of VHL-associated-RCC, central nervous system (CNS) hemangioblastomas, or pNET, not requiring immediate surgery.
[e] Jonasch E, Donskov F, Iliopoulos O, et al. Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease. N Engl J Med 2021;385:2036-2046.
[f] Pazopanib was associated with a >50% objective response rate in renal lesions in a 31-patient phase II study. Jonasch E, McCutcheon IE, Gombos DS, et al. Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-centre, phase 2 trial. Lancet Oncol 2018;19:1351-1359.

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

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

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

Table 2. **AJCC Prognostic Groups**

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

Table 3. **Histologic Grade (G)**

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

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ABBREVIATIONS

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

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.

Discussion

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

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Overview

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

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

Analysis of the SEER database indicates that RCC incidence has been rising on average 0.6% each year and death rates have been falling on average 1.6% each year from 2010 through 2019.[3] The 5-year survival rate for localized RCC has increased from 88.4% (during 1992–1995) to 93.0% (during 2012–2018) and for advanced disease from 7.3% (during 1992–1995) to 15% (during 2012–2018).[13] The most important prognostic determinants of 5-year survival are the tumor stage, grade, local extent of the tumor, presence of regional nodal metastases, and evidence of metastatic disease at presentation.[14-23] RCC primarily metastasizes to the lung, bone, liver, lymph nodes, adrenal gland, and brain.[10,24,25]

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

Guidelines Update Methodology

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

Literature Search Criteria

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

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

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

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

Sensitive/Inclusive Language Usage

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

Initial Evaluation and Staging

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

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

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

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

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

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

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

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

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

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

Treatment of Localized Disease

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

Nephron-Sparing Surgery and Radical Nephrectomy

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

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

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

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

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

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

Lymph Node Dissection

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

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

Adrenalectomy

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

Active Surveillance and Ablative Techniques

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

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

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

Management of Stage I (T1a) Disease

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

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

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

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

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

Management of Stage I (T1b) Disease

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

Management of Stage II and III Disease

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

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

Adjuvant Treatment for Clear Cell, High-Risk Localized RCC

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

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

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

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

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

Immune checkpoint inhibitors (ICIs) that target programmed death receptor-1 (PD-1) on T cells have also been investigated in the adjuvant setting. The phase III multicenter, randomized, double-blind, placebo-controlled KEYNOTE-564 trial investigated the use of pembrolizumab versus placebo in 994 patients with locoregional RCC with a clear-cell histology and an intermediate-to-high or high risk of recurrence (ie, tumor stage 2 with nuclear grade 4 or sarcomatoid differentiation, tumor stage 3 or higher, regional lymph node metastasis) after nephrectomy, or stage M1 with NED (no evidence of disease) status after nephrectomy and resection of metastatic lesions.[89] DFS was noted in 77.3% of patients treated with pembrolizumab as compared to 68.1% of patients given placebo at 24 months (HR for recurrence or death, 0.68; 95% CI, 0.53–0.87; $P = .002$). OS at 24 months was estimated to be 96.6% in pembrolizumab-treated patients versus 93.5% in the placebo group. Grade 3 or higher AEs occurred in 32.4% of pembrolizumab-treated patients versus 17.7% of those who received placebo.[89]

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

Follow-up After Treatment of Localized Disease

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

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

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

Follow-up During Active Surveillance for Stage T1a

For follow-up during active surveillance, the panel recommends an annual history and physical examination and annual laboratory tests as clinically indicated. In order to study the growth rate of the tumor, the panel recommends abdominal imaging (CT or MRI with contrast) within 6 months from initiation of active surveillance; subsequent imaging (with CT, MRI, or ultrasound [US]) may be performed annually thereafter. All three modalities (US, CT, and MRI) have been found to accurately predict pathologic tumor size in a retrospective analysis.[93] Therefore, best clinical judgment should be used in choosing the imaging modality. The panel recommends chest x-ray or chest CT at baseline and annually as clinically indicated to assess for pulmonary metastases. Repeat chest imaging can be considered if intervention is being contemplated. The panel notes that follow-up may be individualized based on surgical status, treatment schedules, side effects, comorbidities, and symptoms.

Follow-up After Ablative Therapy for Stage T1a

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

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

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

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

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

Follow-up for Patients with Stage III RCC

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

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

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

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

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

Management of Relapsed or Stage IV Disease

Prognostic Models for Metastatic Disease

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

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

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

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

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

Surgical Options for Patients with Relapsed or Stage IV Disease

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

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

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

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

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

Systemic Therapy Options for Patients with Relapsed or Stage IV Disease

Targeted therapy utilizing TKIs, and/or anti-VEGF antibodies, has been widely used in first- and second-line treatments. Agents targeting the mammalian target of rapamycin (mTOR) are also used in highly selected settings. A number of targeted agents have been approved by the FDA for the treatment of advanced RCC in the first and/or subsequent lines of therapy. ICIs provided a revolution in treatment options. Checkpoint antibodies alter the interaction between immune cells and antigen-presenting cells, including tumor cells. These agents can augment an anti-tumor immune response and have shown promise in a number of tumor indications.

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

NCCN Categories of Preference

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

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

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

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

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

Preferred Regimens

Axitinib with Pembrolizumab (All Risk Groups)

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

Cabozantinib with Nivolumab (All Risk Groups)

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

Lenvatinib with Pembrolizumab (All Risk Groups)

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

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

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

Ipilimumab is a monoclonal antibody that selectively blocks the interaction between the negative regulator cytotoxic T-lymphocyte antigen 4 (CTLA-4; expressed early on activated T cells) and its ligands CD80/CD86 (expressed on antigen-presenting cells); nivolumab's mechanism of action was described previously. In April 2018, the FDA approved ipilimumab in combination with nivolumab for first-line treatment of patients with poor-/intermediate-risk advanced RCC.[119] Data from the randomized phase III CheckMate 214 trial, which supported the FDA approval, compared combination ipilimumab/nivolumab followed by nivolumab monotherapy with sunitinib monotherapy in patients with advanced RCC.[120] The study's coprimary endpoints were ORR, OS, and PFS in intermediate- and poor-risk patients only; exploratory analyses of data in favorable-risk patients were reported separately (see *Table 1* and ccRCC: *First-Line, Other Recommended Regimens*). In intermediate-/poor-risk patients, combination ipilimumab/nivolumab led to a higher ORR and CR rate versus sunitinib monotherapy. Median PFS did not meet the prespecified threshold, and was not statistically significant between the two treatment arms. Treatment-related AEs occurred in 93% of patients in the ipilimumab/nivolumab group and 97% of patients in the sunitinib group; grade 3 or 4 events occurred in 46% and 63%, respectively. AEs led to treatment discontinuation in 22% and 12% of patients receiving ipilimumab/nivolumab and sunitinib, respectively. Treatment-related deaths occurred in 8 patients receiving the combination therapy and 4 patients receiving sunitinib. Thirty-five percent of patients who developed immune-mediated AEs after ipilimumab/nivolumab treatment received high-dose steroids.[120] Based on these data, the panel recommends first-line ipilimumab/nivolumab as a category 1, preferred treatment option for poor- and intermediate-risk patients with ccRCC.

Cabozantinib (Poor-/Intermediate-Risk Groups)

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

Other Recommended Regimens

Axitinib with Avelumab (All Risk Groups)

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

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

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

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

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

Pazopanib (All Risk Groups)
Pazopanib is an oral multitargeted TKI/angiogenesis inhibitor of VEGFRs, PDGFR-α and -β, and stem cell factor receptor (c-KIT). The drug's safety and efficacy were evaluated in an open-label phase III study. Patients with advanced ccRCC who received 0–1 prior treatment received either pazopanib or placebo (see *Table 1* for efficacy data). PFS was significantly longer and ORR was significantly higher with pazopanib versus placebo in the treatment-naïve sub-population,[126] but there was no difference in OS between the two groups.[127] Notable grade 3 toxicity was hepatotoxicity, indicated by elevated levels of alanine (30%) and aspartate (21%) transaminase.[126] Therefore, it is critical to monitor liver function before and during treatment with the drug.

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

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

Useful in Certain Circumstances Treatments

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

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

Axitinib (All Risk Groups)

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

High-Dose IL-2 (All Risk Groups)

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

Temsirolimus (Poor-/Intermediate-Risk Patients)

Temsirolimus is an inhibitor of the mTOR protein. The randomized, open-label phase III ARCC study enrolled previously untreated patients with advanced RCC who had three or more unfavorable prognostic factors.[141] Patients received IFN-α alone, temsirolimus alone, or the combination of temsirolimus and IFN-α. Those who received temsirolimus alone showed improvement in OS and median PFS over those receiving IFN-α alone or combination therapy. Based on these data, the panel has included first-line temsirolimus as a category 3, useful in certain circumstances option for poor- and intermediate-risk patients with ccRCC.

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

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

Cabozantinib

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

statistically significant increase in OS in the cabozantinib arm versus the everolimus arm.[143,144]

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

Lenvatinib with Everolimus

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

Nivolumab

In the randomized phase III CheckMate 025 trial, patients with advanced ccRCC who were previously treated with one or more lines of therapy (excluding mTOR inhibitors) received either nivolumab or everolimus. See *Table 2* for efficacy data. Patients receiving nivolumab had significantly longer OS and significantly higher ORR than those receiving everolimus.[150] An independent analysis was carried out to determine the efficacy of nivolumab-based baseline factors such as number and location of metastases, risk group, number of prior therapies, and specific prior therapies (ie, sunitinib, pazopanib, IL-2); a consistent OS benefit and ORR were observed across all baseline factors.[151] Based on these data, the panel has included nivolumab as a category 2A, subsequent therapy option for patients with ccRCC who have not received any prior IO therapy.

Axitinib

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

Axitinib with Pembrolizumab

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

Cabozantinib with Nivolumab

Apolo et al 2020[153] 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[154] reported a pooled analysis of the phase I dose-finding cohort and seven subsequent expansion cohorts, which included 16 patients with metastatic RCC. See *Table 2* for efficacy data. In these patients, median OS was 38.6 months (95% CI, 19.4–not estimable [NE]). The panel added cabozantinib/nivolumab as a category 2A, other recommended option for patients who are IO therapy naïve and useful in certain circumstances for patients with prior IO therapy.

Ipilimumab with Nivolumab

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

Lenvatinib with Pembrolizumab

The ongoing phase II KEYNOTE-146 trial included three groups of patients: treatment-naïve; those who had previously received at least one line of treatment that did not include anti–PD-1 or anti–PD-L1 ICIs; and those who had previously received at least one anti–PD-1 or anti–PD-L1 ICI. See *Table 2* for efficacy data. Treatment-naïve patients had the highest ORR and the longest PFS; ORR and PFS were comparable in the ICI-naïve and ICI treatment-experienced groups. Median OS was only met in the ICI-naïve group.[156] Based on these data, the panel considers lenvatinib/pembrolizumab a category 2A, other recommended option for patients who are IO therapy naïve and useful in certain circumstances option for patients with prior IO therapy.

Pazopanib

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

Sunitinib

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

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

Tivozanib

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

Axitinib with Avelumab

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

Everolimus

Everolimus (RAD001) is an orally administered mTOR inhibitor. In the randomized phase III RECORD-1 trial, everolimus was compared with placebo for the treatment of metastatic RCC in patients whose disease had progressed on treatment with sunitinib or sorafenib. The median PFS was significantly longer for everolimus versus placebo, but OS was similar between the two groups.[167,168] Everolimus is listed as a category 2A, useful in certain circumstances subsequent therapy option for patients with ccRCC regardless of their prior IO therapy status.

Bevacizumab

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

High-Dose IL-2 (for selected patients)

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

Sorafenib

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

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.[177] The panel considers temsirolimus a category 2B, useful in certain

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

Belzutifan

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

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

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

nccRCC: Preferred Regimens

Cabozantinib

The randomized phase II SWOG 1500 trial compared the MET-targeted TKIs cabozantinib, crizotinib, and savolitinib with standard-of-care sunitinib in patients with advanced papillary RCC who had previously received up to 1 previous systemic therapy, excluding VEGF- and MET-targeted TKIs. Assignment to the crizotinib and savolitinib arms was halted due to results of a prespecified futility analysis.[180] See *Table 3* for efficacy data. Patients receiving cabozantinib had significantly longer PFS and a higher ORR than those receiving sunitinib. Based on these data, the panel included cabozantinib as a category 2A, preferred option for patients with nccRCC.

Sunitinib

Two recent randomized phase II studies compared first-line sunitinib with first-line everolimus in patients with nccRCC. See *Table 3* for efficacy data. While data from the ASPEN trial[181] suggested that patients receiving sunitinib had significantly longer PFS than those receiving everolimus, data from the ESPN trial[182] suggested that both OS and PFS were similar between the two groups.

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

nccRCC: Other Recommended Regimens

Lenvatinib with Everolimus

Extrapolating on data from the phase III lenvatinib/everolimus trial in patients with ccRCC[148] (see *ccRCC: Subsequent, Preferred Regimens*), the panel added the combination therapy as a category 2A, other recommended regimen for patients with nccRCC.

They also reviewed data[184] from an ongoing single-arm phase II trial (ie, NCT02915783) enrolling patients with unresectable advanced or metastatic nccRCC who had not previously received prior systemic therapy; all patients in the trial received combination lenvatinib/everolimus. See *Table 3* for efficacy data. Authors reported that ORR was 26% (95% CI, 12–45). Eight patients in the trial achieved a PR (papillary, n = 3; chromophobe, n = 4; unclassified, n = 1); no patients had a CR. The median duration of response was NE. Eighteen patients (58.1%) had SD, and the clinical benefit rate (CR + partial response [PR] + durable SD [duration ≥23 weeks]) was 61% (95% CI, 42–78). The median PFS was 9.2 months (95% CI, 5.5–NE) and OS was 15.6 months (95% CI, 9.2–NE). While the panel conceded that the number of enrolled patients was small, they generally felt that lenvatinib/everolimus treatment led to improved patient outcomes across all nccRCC subtypes.

Nivolumab

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

Nivolumab with Cabozantinib

Two separate patient cohorts defined by nccRCC histology in a phase II open-label trial received nivolumab/cabozantinib combination.[187] ORR for patients with papillary, unclassified, or translocation RCC was 48% with a median follow-up time of 13.1 months. Median PFS was 12.5 months (95% CI, 6.3–16.4) and median OS was 28 months (95% CI, 16.3–NE). Study of patients with chromophobe RCC closed early due to the lack of efficacy. Based on these results, the panel added nivolumab/cabozantinib under other recommended options as first or subsequent-line treatment of relapse or stage IV nccRCC.

Pembrolizumab

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

nccRCC: Useful in Certain Circumstances Regimens

Axitinib

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

Bevacizumab

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

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

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

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

Bevacizumab with Everolimus

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

Erlotinib

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

Everolimus

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

Nivolumab with Ipilimumab

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

Pazopanib

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

Temsirolimus

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

Additional Treatment Options for Rare Types of nccRCC

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

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

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

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

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

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

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

Supportive Care

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

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

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

The role of bone-modifying agents such as bisphosphonates (eg, zoledronic acid) has been established in patients with various malignancies.[220,221] The newer bone-modifying agent approved for use in patients with RCC that has metastasized to the bone is the RANK-L inhibitor, denosumab. A phase III randomized trial directly compared the development of SREs on either denosumab or zoledronic acid in patients with multiple myeloma or bone metastases with a solid tumor (excluding breast or prostate cancer). The study enrolled 1776 patients with bone metastases from a wide range of cancer types, including patients with RCC (6%) not previously treated with a bisphosphonate.[222] Denosumab was reported to be non-inferior to zoledronic acid in delaying time to first on-study SRE (HR, 0.84; 95% CI, 0.71–0.98; P = .0007).[222]

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

Hereditary RCC Syndromes

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

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

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

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

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

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

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

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

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

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

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

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

The panel also provides surgical recommendations for the majority of the included hereditary RCC syndromes, which are based on published data and/or the subcommittee's real-world experience in treating patients with these syndromes. In order to develop these recommendations, they carefully weighed the potential morbidity and mortality of surgical treatment against the potential aggressiveness of each of the syndromes. They agreed that patients with BHDS, HPRC, and TSC may benefit from more conservative treatment, such as nephron-sparing surgery or ablative therapies,[231,232] while patients with HLRCC should undergo total radical nephrectomy.[191] The panel's recommendations for surgical treatment of PGL/PCC vary by tumor size and histology: those with smaller, less aggressive tumors may be eligible for partial nephrectomy, while those with larger, more aggressive tumors (eg, high-grade, sarcomatoid) should undergo radical nephrectomy.[233] Tumor size also factored into the panel's surgical recommendations for patients with VHL disease; they noted that these patients are likely to undergo multiple surgical resections during their lifetime that may contribute to chronic and progressive renal failure. Thus, the timing of surgical intervention must be carefully determined in order to limit the development of metastases and morbidity associated with surgical intervention. They agreed that only patients with VHL disease with tumors approaching 3 cm in diameter should undergo partial nephrectomy (or ablative therapy if nephrectomy is contraindicated).[232,234]

Kidney-Specific Systemic Therapy for Patients with Confirmed Hereditary RCC

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

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

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

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

Data Summary

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

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

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

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

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	Median PFS (months)	Median OS (months)
CLEAR Motzer et al 2021[118]	**Lenvatinib + pembrolizumab**	355	Favorable-, intermediate-, or poor-risk, systemic therapy-naïve, advanced ccRCC; Karnofsky PS ≥70%	27	ORR Len/Pem: 71 Len/Ev: 54 Sunitinib: 36 ORR, Len/Pem vs. Sunitinib RR: 1.97 (95% CI, 1.69–2.29) ORR, Len/Ev vs. Sunitinib RR: 1.48 (95% CI, 1.26–1.74) CR Len/Pem: 16 Lev/Ev: 10 Sunitinib: 4	Len/Pem: 23.9 (95% CI, 20.8–27.7) Len/Ev: 14.7 (95% CI,11.1–16.7) Sunitinib: 9.2 (95% CI, 6.0–11.0) Len/Pem vs. Sunitinib HR, 0.39 (95% CI, 0.32–0.49) *P* < .001 Len/Ev vs. Sunitinib HR, 0.65 (95% CI, 0.53–0.80) *P* < .001	Len/Pem: NR Len/Ev: NR Sunitinib: NR Len/Pem vs. Sunitinib HR, 0.66 (95% CI, 0.49–0.88) *P* = .005 Len/Ev vs. Sunitinib HR, 1.15 (95% CI, 0.88–1.50) *P* = .30
	Lenvatinib + everolimus	357					
	Sunitinib	357					
Monotherapy							
VEG105192 Sternberg et al 2013[127] (OS data) Sternberg et al 2010[126] (PFS and ORR data)	**Pazopanib**	290	Favorable-, intermediate-, or poor-risk, locally advanced or metastatic ccRCC; ECOG PS 0–1 Note: Of 435 enrolled patients, 202 received prior cytokine treatment and 233 were systemic therapy-naïve. Data were reported separately. See Table 2 for data for patients who received prior treatment.	Median NR; Up to 24 months for primary outcome	Pazopanib: 32 (95% CI, 24–39) Placebo: 4 (95% CI, 0–8)	Pazopanib: 11.1 Placebo: 2.8 HR, 0.40 (95% CI, 0.27–0.60) *P* < .0001	Pazopanib: 23 Placebo: 24 HR, 1.01 (95% CI, 0.72–1.42) *P* value NR
	Placebo	145					

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

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

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

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
Phase II study Motzer et al 2016[149] Motzer et al 2015[148]	**Lenvatinib/everolimus**	51	Favorable-, intermediate-, or poor-risk advanced or metastatic ccRCC; received at least one VEGFR-targeted TKI with progression within 9 months of treatment; ECOG PS 0–1	17-19; varied by group	Len/Ev: 43 Ev: 6 Len: 27 Len/Ev vs. Len *P* < .0001 Len vs. Ev *P* = .0067	Len/Ev: 14.6 (95% CI, 5.9–20.1) Ev: 5.5 (95% CI, 3.5–7.1) Len: 7.4 (95% CI, 5.6–10.2) Len/Ev vs. Ev HR, 0.40 (95% CI, 0.24–0.68) *P* = .0005 Len/Ev vs. Len HR, 0.66 (95% CI, 0.39–1.10) *P* = .12 Len vs. Ev HR, 0.61 (95% CI, 0.39–0.98) *P* = .048	Len/Ev: 25.5 (95% CI, 16.4–NE) Ev: 15.4 (95% CI, 11.8–19.6) Len: 19.1 (95% CI, 13.6–26.2) Len/Ev vs. Ev HR, 0.51 (95% CI, 0.30–0.88) *P* = .024 Len vs. Len/Ev HR, 0.75 (95% CI, 0.43–1.30) *P* = .32 Len vs. Ev HR, 0.68 (95% CI, 0.41–1.14) *P* = .12
	Everolimus	50					
	Lenvatinib	52					
KEYNOTE-146 Lee et al 2021[156]	**Lenvatinib/pembrolizumab, previously treated but ICI-naïve (2+L ICI-naïve)**	17	Favorable-, intermediate-, or poor-risk metastatic ccRCC; ECOG PS 0–1	6-51 months; varied by outcome	Week 24 2+L, ICI-naïve: 41 2+L, ICI-TE: 56 TN: 73 Overall 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					

Trial/Author	Regimen	No. of Patients	Patient Characteristics	Median Follow-up (months)	ORR (%)	PFS (months)	OS (months)
Monotherapy							
AXIS Motzer et al 2013[152] Rini et al 2011[136] Note: Only the most recent data are shown.	**Axitinib**	361	Favorable-, intermediate-, or poor-risk, systemic therapy-naïve metastatic ccRCC; ECOG PS 0–1	Up to 36 months	Axi: 19 Sor: 9 *P* = .0001	Axi: 8.3 (95% CI, 6.7–9.2) Sor: 5.7 (95% CI, 4.7–6.5) HR, 0.67 (95% CI, 0.55–0.78) *P* < .0001	Axi: 20.1 (95% CI, 16.7–23.4) Sor: 19.2 (95% CI, 17.5–22.3) HR, 0.97 (95% CI, 0.80–1.17) *P* = .37
	Sorafenib	362					
METEOR Motzer et al 2018[144] Choueiri et al 2016[143] Choueiri et al 2015[142] Note: Only the most recent outcome data are shown.	**Cabozantinib**	330	Favorable-, intermediate-, or poor-risk advanced or metastatic ccRCC; received at least one VEGFR-targeted TKI with progression within 6 months of treatment; Karnofsky PS ≥70%	OS: 22[144] ORR, PFS: 19[143]	Cabo: 17 Ev: 3 *P* < .0001	Cabo: 7.4 (95% CI, 6.6–9.1) Ev: 3.9 (95% CI, 3.7–5.1) HR, 0.51 (95% CI, 0.41–0.62) *P* < .0001	Cabo: 21.4 Ev: 17.1 HR, 0.70 (95% CI, 0.58–0.85) *P* = .0002
	Everolimus	328					
CheckMate 025 Motzer et al 2015[150]	**Nivolumab**	406	Favorable-, intermediate-, or poor-risk advanced or metastatic ccRCC; received 1-2 prior antiangiogenic therapies (except mTOR inhibitors); Karnofsky PS ≥70%	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) HR, 0.88 (95% CI, 0.75–1.03) *P* = .11	Nivo: 25.0 (95% CI, 21.8–NE) Ev: 19.6 (95% CI, 17.6–23.1) HR, 0.73 (95% CI, 0.57–0.93) *P* = .002
	Everolimus	397					
VEG105192 Sternberg et al 2013[127] (OS data) Sternberg et al 2010[126] (PFS and ORR data)	**Pazopanib**	290	Favorable-, intermediate-, or poor-risk locally advanced or metastatic ccRCC; ECOG PS 0–1 Note: Of 435 enrolled patients, 202 received prior cytokine treatment and 233 were systemic therapy-naïve. Data were reported separately. See Table 1 for data for patients who were systemic therapy-naïve.	Median NR; Up to 24 months for primary outcome	Paz: 29 Placebo: 3	Paz: 7.4 Placebo: 4.2 HR, 0.54 (95% CI, 0.35–0.84) *P* < .001	Paz: 23 Placebo: 19 HR, 0.82 (95% CI, 0.57–1.16) *P* value NR
	Placebo	145					

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

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

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

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

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