



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Kidney Cancer

Version 4.2019 — April 25, 2019

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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.

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical_trials/clinicians.html](#).

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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Updates in Version 4.2019 of the NCCN Guidelines for Kidney Cancer from from Version 3.2019 include:

[KID-4](#)

- Relapse or Stage IV: First-line Therapy for Clear Cell Histology
 - ▶ Preferred regimens for Favorable risk:
 - ◊ Axitinib + pembrolizumab was added as a category 2A recommendation.
 - ◊ Pazopanib changed from a category 1 recommendation to a category 2A recommendation.
 - ◊ Sunitinib changed from a category 1 recommendation to a category 2A recommendation.
 - ▶ Preferred regimen for Poor/intermediate risk:
 - ◊ Axitinib + pembrolizumab was added as a category 1 recommendation.
- Relapse or Stage IV: Subsequent Therapy for Clear Cell Histology
 - ▶ Other recommended regimens:
 - ◊ Axitinib + pembrolizumab was added as a category 2A recommendation.

Updates in Version 3.2019 of the NCCN Guidelines for Kidney Cancer from from Version 2.2019 include:

[MS-1](#)

The discussion section was updated to reflect the changes in the algorithm.

Updates in Version 2.2019 of the NCCN Guidelines for Kidney Cancer from from Version 1.2019 include:

[KID-1](#)

- Stage
 - ▶ Stage I (pT1a) was clarified by removing the "p", as "Stage I (T1a)." Also for KID-B 1 of 4.
 - ▶ Stage I (pT1b) was clarified by removing the "p", as "Stage I (T1b)."

Updates in Version 1.2019 of the NCCN Guidelines for Kidney Cancer from from Version 4.2018 include:

[KID-1](#)

- Initial workup
 - ▶ 4th bullet was revised, "Abdominal ± pelvic CT or ~~abdominal~~ MRI."
 - ▶ 7th bullet was revised, "If urothelial carcinoma suspected (eg, central mass), consider urine cytology, ureteroscopy or *percutaneous biopsy*."
- Footnote a was change from, "Imaging with contrast when clinically indicated" to "Contrast is strongly preferred, such as a renal protocol."
- Footnote c was added, "If metastatic disease is present or the patient cannot tolerate ureteroscopy."

[KID-3](#)

- Relapse or Stage IV
 - ▶ "Predominant" was removed from "clear cell histology"
 - ▶ First-line therapy for both clear cell and non-clear cell histology was revised with the following format
Clinical trial
or
See First-Line Therapy
or
Metastasectomy or SBRT or ablative techniques for oligometastatic disease
and
Best supportive care

- After first-line therapy for clear cell histology, the subsequent therapy was revised with the following format
Clinical trial
or
See Subsequent Therapy for Clear Cell Histology (KID-4)
and
Best supportive care
- Footnote i was revised, "Best supportive care can include palliative RT including SBRT, ~~metastasectomy, ablative techniques for oligometastatic disease~~, bisphosphonates, or RANK ligand inhibitors for bony metastases."



Updates in Version 1.2019 of the NCCN Guidelines for Kidney Cancer from from Version 4.2018 include:

[KID-4](#)

- For both First-line therapy and Subsequent therapy for clear cell histology, the Categories of Preference were applied.
- First-line therapy
- For both favorable risk and poor/intermediate, axitinib was changed from a category 2A to category 2B designation.
- Subsequent therapy
 - Sorafenib was changed from a category 2A to category 2B designation.
- Footnote was removed, "Based on the results of phase III trials, eligible patients should preferentially receive this agent over everolimus. See Discussion."
 - For favorable risk, cabozantinib was added as an other recommended regimen with a category 2B designation.

[KID-5](#)

- For Systemic therapy for non-clear cell histology, the Categories of Preference were applied.
 - Sorafenib was removed as an option.
- Footnote o was revised from "Partial responses have been observed for cytotoxic chemotherapy (carboplatin + gemcitabine, carboplatin + paclitaxel, or cisplatin + gemcitabine) with collecting duct or medullary subtypes" to "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."

[KID-A](#)

- 1st bullet, 3rd sub-bullet was added, "Patients at relative risk for developing progressive chronic kidney disease due to young age or medical risk factors (hypertension, diabetes, nephrolithiasis)."
- 5th bullet was revised, "Special teams or referral to high-volume centers may be required for extensive..."
- 6th bullet and subsequent sub-bullets were added, "Active surveillance is

an option for the initial management of patients with clinical stage T1 renal lesions, for example:

- Patients with small renal masses <2 cm given the high rates of benign tumors and low metastatic potential of these masses.
- 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 growth (eg, 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."
- 7th bullet and subsequent sub-bullets regarding ablative techniques was extensively updated
 - Thermal ablation (eg, cryosurgery, radiofrequency ablation) is an option for the management of patients with clinical stage T1 renal lesions.
 - ◊ Thermal ablation is an option for masses <3cm, but may also be an option for larger masses in select patients. Ablation in masses >3cm is associated with higher rates of local recurrence/persistence and complications.
 - ◊ Biopsy of small lesions confirms a diagnosis of malignancy for surveillance, cryosurgery, and radiofrequency ablation strategies.
 - ◊ Ablative techniques are associated with a higher local recurrence rate than conventional surgery and may require multiple treatments to achieve the same local oncologic outcomes.
 - References a and b were updated.

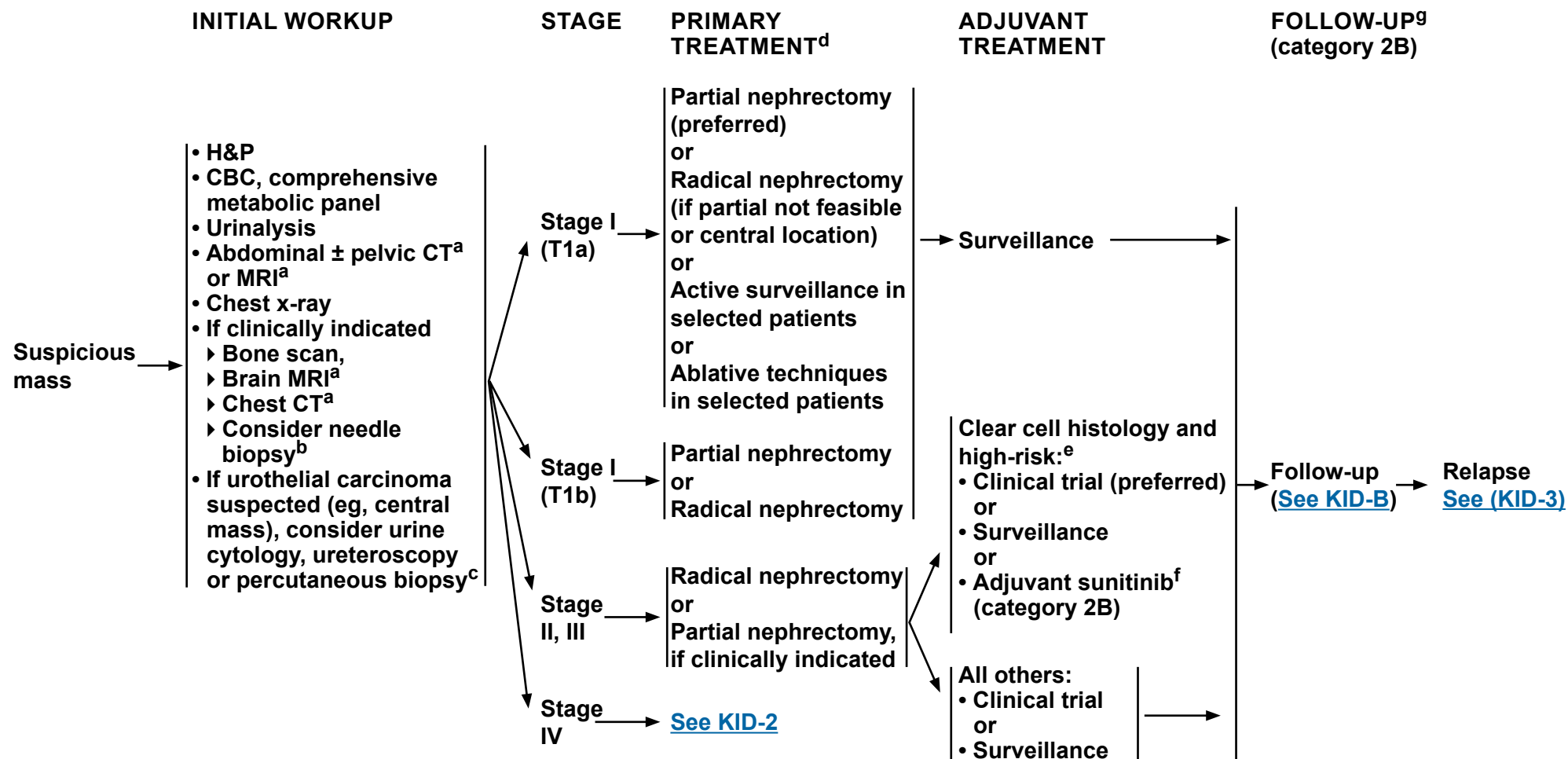
[KID-B 3 of 4](#)

- Follow-up After a Radical Nephrectomy
 - 4th bullet, 1st sub-bullet, "Baseline chest CT within 3–6 mo after radical nephrectomy with continued imaging (*CT preferred or chest x-ray*)..."



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^aContrast is strongly preferred, such as a renal protocol.

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

^cIf metastatic disease is present or the patient cannot tolerate ureteroscopy.

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

^eHigh-risk defined as: tumor stage 3 or higher, regional lymph-node metastasis, or both.

^fDosing of adjuvant sunitinib: 50 mg per day - 4 weeks on, 2 weeks off for 1 year.

^gNo single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

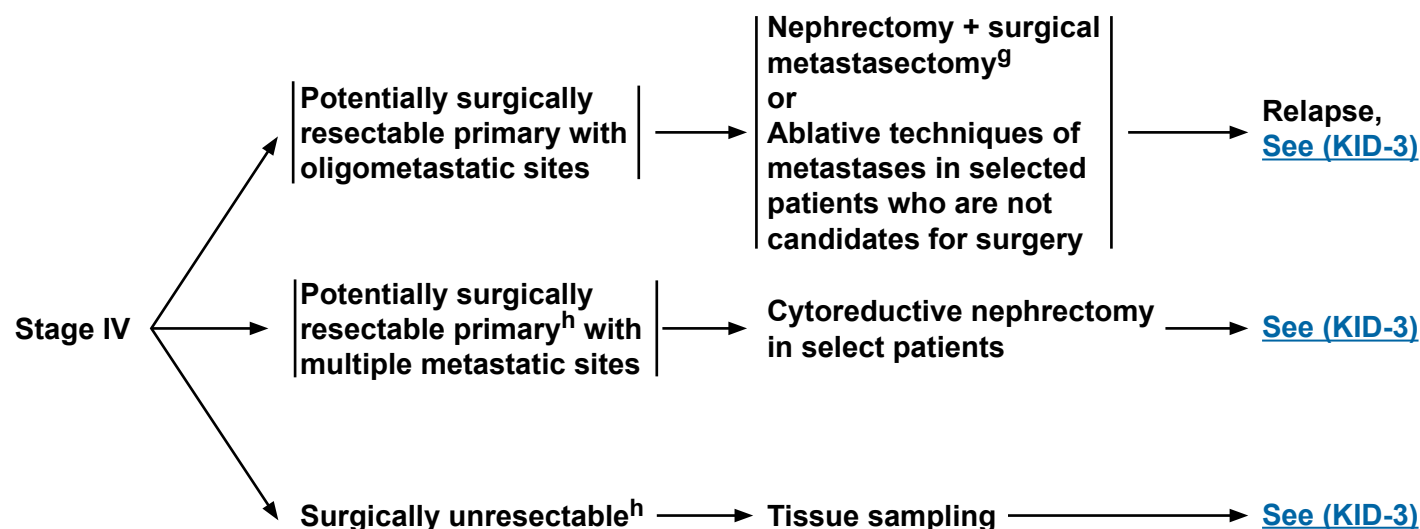
Note: All recommendations are category 2A unless otherwise indicated.

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.



STAGE

PRIMARY TREATMENT^d



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

^gNo single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

^hIndividualize treatment based on symptoms and extent of metastatic disease.

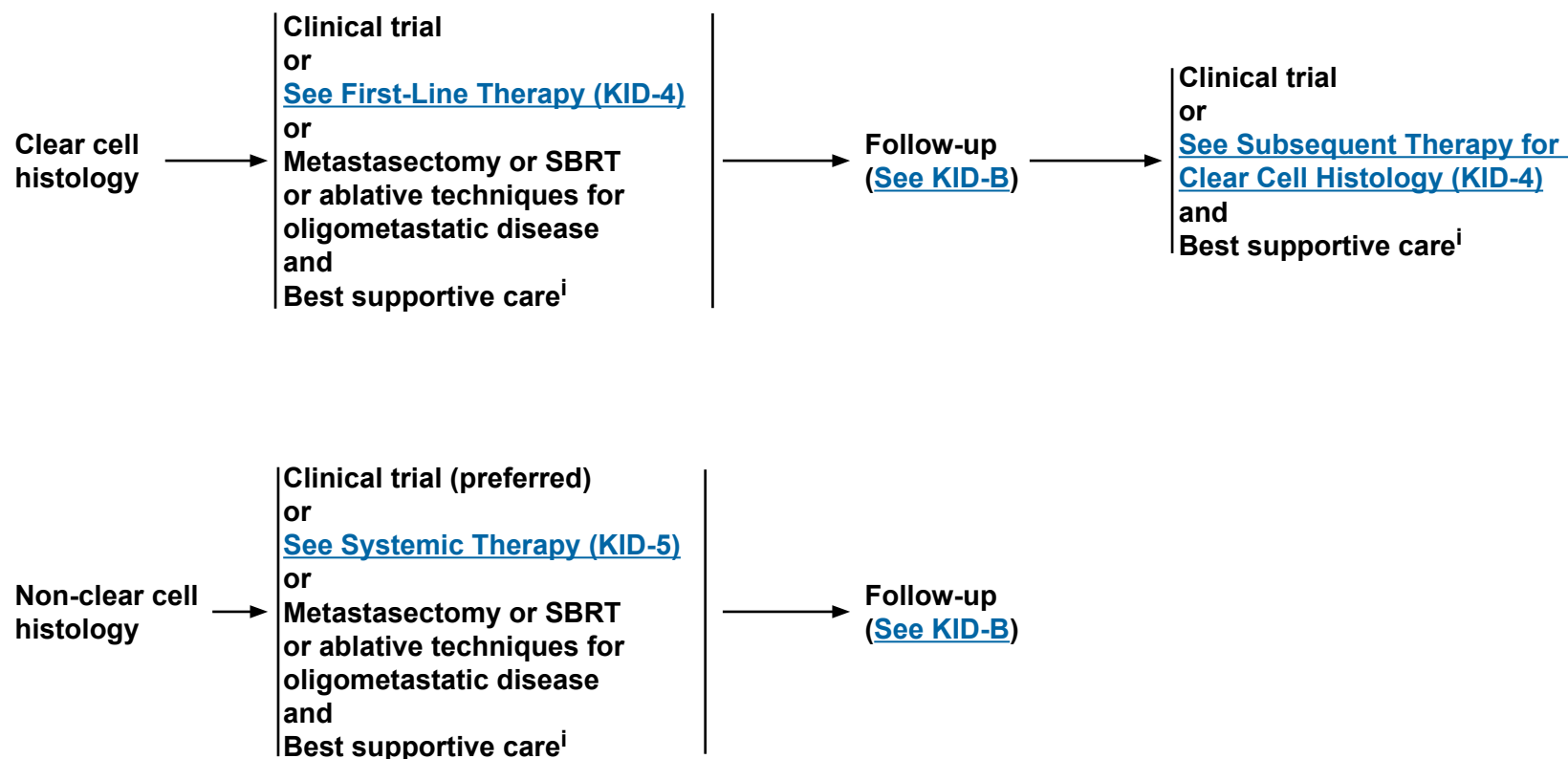
Note: All recommendations are category 2A unless otherwise indicated.

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RELAPSE OR STAGE IV

TREATMENT



ⁱBest supportive care can include palliative RT including stereotactic body radiation therapy (SBRT), bisphosphonates, or RANK ligand inhibitors for bony metastases.

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RELAPSE OR STAGE IV: FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
	Preferred regimens	Other recommended regimens	Useful under certain circumstances
Favorable risk^j	<ul style="list-style-type: none"> • Axitinib + pembrolizumab • Pazopanib • Sunitinib 	<ul style="list-style-type: none"> • Ipilimumab + nivolumab • Cabozantinib (category 2B) 	<ul style="list-style-type: none"> • Active surveillance^k • Axitinib (category 2B) • Bevacizumab + interferon alfa-2b (category 1) • High-dose IL-2^l
Poor/ intermediate risk^j	<ul style="list-style-type: none"> • Ipilimumab + nivolumab (category 1) • Axitinib + pembrolizumab (category 1) • Cabozantinib 	<ul style="list-style-type: none"> • Pazopanib (category 1) • Sunitinib (category 1) 	<ul style="list-style-type: none"> • Axitinib (category 2B) • Bevacizumab + interferon alfa-2b (category 1) • High-dose IL-2^l • Temsirolimus (category 1)^m

RELAPSE OR STAGE IV: SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY ⁿ		
Preferred regimens	Other recommended regimens	Useful under certain circumstances
<ul style="list-style-type: none"> • Cabozantinib (category 1) • Nivolumab (category 1) • Ipilimumab + nivolumab 	<ul style="list-style-type: none"> • Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab • Everolimus • Pazopanib • Sunitinib 	<ul style="list-style-type: none"> • Bevacizumab (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients^l (category 2B) • Temsirolimus (category 2B)^m

^j[See Risk Models to Direct Treatment \(IMDC criteria\) \(KID-C\).](#)^kRini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol 2016;17:1317-1324.^lPatients with excellent performance status and normal organ function.^m[See Risk Models to Direct Treatment \(Predictors of Short Survival Used to Select Patients for Temsirolimus\) \(KID-C\).](#)ⁿIn clear cell and non-clear cell RCC with predominant sarcomatoid features, gemcitabine + doxorubicin (category 2B) and gemcitabine + sunitinib (category 2B) have shown benefit.**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.**



RELAPSE OR STAGE IV: SYSTEMIC THERAPY NON-CLEAR CELL HISTOLOGY ^{n,o}		
Preferred regimens	Other recommended regimens	Useful under certain circumstances
<ul style="list-style-type: none"> • Clinical trial • Sunitinib 	<ul style="list-style-type: none"> • Cabozantinib • Everolimus 	<ul style="list-style-type: none"> • Axitinib • Bevacizumab • Erlotinib • Lenvatinib + everolimus • Nivolumab • Pazopanib • Bevacizumab + erlotinib for selected patients with advanced papillary RCC including HLRCC • Bevacizumab + everolimus • Temsirolimus (category 1 for poor-prognosis risk group;^m category 2A for other risk groups)

HLRCC: Hereditary leiomyomatosis and renal cell cancer^m[See Risk Models to Direct Treatment \(Predictors of Short Survival Used to Select Patients for Temsirolimus\) \(KID-C\).](#)ⁿIn clear cell and non-clear cell RCC with predominant sarcomatoid features, gemcitabine + doxorubicin (category 2B) and gemcitabine + sunitinib (category 2B) have shown benefit.^oFor 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.**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 SURGERY

- Nephron-sparing surgery (partial nephrectomy) is appropriate in selected patients, for example:
 - ▶ 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 is recommended for patients with adenopathy on preoperative imaging or palpable/visible adenopathy at time of surgery.
- If adrenal gland is uninvolved, resection may be omitted.
- Special teams or referral to high-volume centers may be required for extensive inferior vena cava involvement.
- Active surveillance is an option for the initial management of patients with clinical stage T1 renal lesions, for example:
 - ▶ Patients with small renal masses <2 cm given the high rates of benign tumors and low metastatic potential of these masses.
 - ▶ 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 growth (eg, 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.
- Thermal ablation (eg, cryosurgery, radiofrequency ablation) is an option for the management of patients with clinical stage T1 renal lesions.
 - ▶ Thermal ablation is an option for masses <3cm, but may also be an option for larger masses in select patients. Ablation in masses >3cm is associated with higher rates of local recurrence/persistence and complications.
 - ▶ Biopsy of small lesions confirms a diagnosis of malignancy for surveillance, cryosurgery, and radiofrequency ablation strategies.
 - ▶ Ablative techniques are associated with a higher local recurrence rate than conventional surgery and may require multiple treatments to achieve the same local oncologic outcomes.^{a,b}
- Generally, patients who would be candidates for cytoreductive nephrectomy prior to systemic therapy have:
 - ▶ Excellent performance status (ECOG PS <2)
 - ▶ No brain metastasis

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

^bPierorazio 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 (T1a)

Follow-up During Active Surveillance^c

- H&P every 6 mo for 2 y, then annually up to 5 y after diagnosis
- Comprehensive metabolic panel and other tests as indicated every 6 mo for first 2 y, then annually up to 5 y after diagnosis
- Abdominal imaging:
 - ▶ Abdominal CT or MRI within 6 mo of surveillance initiation, then CT, MRI, or US at least annually
- Chest imaging:
 - ▶ Chest x-ray or CT annually to assess for pulmonary metastases, if biopsy positive for RCC
- Pelvic CT or MRI, as clinically indicated
- CT or MRI of head or MRI of spine, as clinically indicated
- Bone scan, as clinically indicated

Follow-up After Ablative Techniques^c

- H&P every 6 mo for 2 y, then annually up to 5 y after diagnosis
- Comprehensive metabolic panel and other tests as indicated every 6 mo for first 2 y, then annually up to 5 y after diagnosis
- Abdominal imaging:
 - ▶ Abdominal CT or MRI at 3–6 mo following ablative therapy unless otherwise contraindicated then CT, MRI, or US annually for 5 y
- Chest imaging:
 - ▶ Chest x-ray or CT annually for 5 y for patients who have biopsy-proven low-risk RCC, nondiagnostic biopsies, or no prior biopsy
- Repeat biopsy:
 - ▶ New enhancement, a progressive increase in size of an ablated neoplasm, new nodularity in or around the treated zone, failure of the treated lesion to regress over time, satellite or port site lesions
- Pelvic CT or MRI, as clinically indicated
- CT or MRI of head or MRI of spine, as clinically indicated
- Bone scan, as clinically indicated

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

^bNo 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 at the discretion of the physician. Further study is required to define optimal follow-up duration.

^cImaging with contrast when clinically indicated.

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

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[Continued](#)

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

Stage I (pT1a) and (pT1b)^c

Follow-up After a Partial or Radical Nephrectomy

- H&P every 6 mo for 2 y, then annually up to 5 y after nephrectomy
- Comprehensive metabolic panel and other tests as indicated every 6 mo for 2 y, then annually up to 5 y after nephrectomy
- Abdominal imaging:
 - ▶ After partial nephrectomy:
 - ◊ Baseline abdominal CT, MRI, or US within 3–12 mo of surgery
 - ◊ If the initial postoperative scan is negative, abdominal CT, MRI, or US may be considered annually for 3 y based on individual risk factors
 - ▶ After radical nephrectomy:
 - ◊ Patients should undergo abdominal CT, MRI, or US within 3–12 mo of surgery
 - ◊ If the initial postoperative imaging is negative, abdominal imaging beyond 12 mo may be performed at the discretion of the physician
- Chest imaging: Chest x-ray or CT annually for 3 y, then as clinically indicated
- Pelvic CT or MRI, as clinically indicated
- CT or MRI of head or MRI of spine, as clinically indicated
- Bone scan, as clinically indicated

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

^bNo 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 at the discretion of the physician. Further study is required to define optimal follow-up duration.

^cImaging with contrast when clinically indicated.

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[Continued](#)

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

Stage II or III

Follow-up After a Radical Nephrectomy^c

- H&P every 3–6 mo for 3 y, then annually up to 5 y after radical nephrectomy and then as clinically indicated thereafter
- Comprehensive metabolic panel and other tests as indicated every 6 mo for 2 y, then annually up to 5 y after radical nephrectomy, then as clinically indicated thereafter
- Abdominal imaging:
 - ▶ Baseline abdominal CT or MRI within 3–6 mo, then CT, MRI, or US (US is category 2B for Stage III), every 3–6 mo for at least 3 y and then annually up to 5 y
 - ▶ Imaging beyond 5 y: as clinically indicated
 - ▶ Site-specific imaging: as symptoms warrant
- Chest imaging:
 - ▶ Baseline chest CT within 3–6 mo after radical nephrectomy with continued imaging (CT preferred) every 3–6 mo for at least 3 y and then annually up to 5 y
 - ▶ Imaging beyond 5 y: as clinically indicated based on individual patient characteristics and tumor risk factors
- Pelvic CT or MRI, as clinically indicated
- CT or MRI of head or MRI of spine, as clinically indicated
- Bone scan, as clinically indicated

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

^bNo 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 at the discretion of the physician. Further study is required to define optimal follow-up duration.

^cImaging with contrast when clinically indicated.

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[Continued](#)

KID-B
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FOLLOW-UP (category 2B)

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 and per patient clinical status. Imaging interval to be adjusted upward and downward according to rate of disease change and sites of active disease
- Consider CT or MRI 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

^cImaging with contrast when clinically indicated.

^dNo single follow-up plan is appropriate for all patients. Follow-up should be individualized based on treatment schedules, side effects, comorbidities, and symptoms.

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

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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 lactate dehydrogenase (LDH) greater than 1.5 times the upper limit of normal (ULN)
- Corrected serum calcium greater than the ULN
- Serum hemoglobin less than the lower limit of normal (LLN)

Prognostic risk groups

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

Predictors of Short Survival Used to Select Patients for Temsirolimus^b

- Lactate dehydrogenase level >1.5 times upper limit of normal
- Hemoglobin level < lower limit of normal
- Corrected serum calcium level >10 mg/dL (2.5 mmol/liter)
- Interval of less than a year from original diagnosis to the start of systemic therapy
- Karnofsky performance score ≤70
- ≥2 sites of organ metastasis

- Poor-prognosis group: ≥3 predictors of short survival

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

Prognostic factors

1. Less than one year from time of diagnosis to systemic therapy
2. Performance status <80% (Karnofsky)
3. Hemoglobin < lower limit of normal (Normal: 120 g/L or 12 g/dL)
4. Calcium > upper limit of normal (Normal: 8.5–10.2 mg/dL)
5. Neutrophil > upper limit of normal (Normal: 2.0–7.0×10⁹/L)
6. 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

^aMotzer 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.

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

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

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

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	N0-N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

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

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 02/16/2019

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability

Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes

Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation)

All recommendations are considered appropriate.

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NCCN Guidelines Version 4.2019

Kidney Cancer

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Overview

An estimated 73,820 Americans will be diagnosed with cancers of the kidney and renal pelvis and 14,770 will die of the disease in the United States in 2019.¹ Renal cell carcinoma (RCC) comprises approximately 3.8% of all new cancers, with a median age at diagnosis of 64 years.² Approximately 85% of kidney tumors are RCC, and approximately 70% of these have a clear cell histology.³⁻⁵ Other less common cell types include papillary, chromophobe, translocation, and Bellini duct (collecting duct) tumors. Medullary renal carcinoma is a rare and aggressive RCC variant that almost exclusively arises in patients who are sickle-cell trait positive.⁶

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 clear cell RCC and other proliferative vascular lesions.⁷⁻¹⁰ Analysis of the SEER database indicates that RCC incidence has been rising on average 0.6% each year and death rates have been falling on average 0.7% each year from 2006 through 2015.² The 5-year survival for localized RCC has increased from 88.4% (during 1992–1995) to 92.6% (during 2007–2013) and for advanced disease from 7.3% (during 1992–1995) to 11.7% (during 2007–2013).¹¹ 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.¹²⁻²¹ RCC primarily metastasizes to the lung, bone, liver, lymph nodes, adrenal gland, and brain.^{8,22,23}

The NCCN Guidelines for Kidney Cancer provide multidisciplinary recommendations for the clinical management of patients with clear cell and non-clear cell RCC. These NCCN Guidelines are intended to assist with clinical decision-making, but they cannot incorporate all possible

clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Medical practitioners should note that unusual patient scenarios (presenting in <5% of patients) are not specifically discussed in these guidelines.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Kidney Cancer, an electronic search of the PubMed database was performed to obtain key literature in 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.²⁴

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 potential relevance of the PubMed search results was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and/or discussed by the panel have been included in this version of the Discussion section (e.g., e-publications ahead of print, meeting abstracts). Any recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

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



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, ultrasound [US]) has become more widespread, the frequency of incidental detection of RCC has increased^{25,26} 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,²⁷ 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) and comprehensive metabolic panel. The metabolic panel may include serum corrected calcium, serum creatinine, liver function studies, and urinalysis.

CT of the abdomen with or without pelvic CT and chest x-ray are essential studies in the initial workup.²⁸ For metastatic evaluation, at the very least, chest radiography must be performed, although chest CT is more accurate than chest radiograph for chest staging.^{29,30} 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.^{31,32} All imaging studies should be performed with contrast, such as renal protocol.

A central renal mass may suggest the presence of urothelial carcinoma; if so, urine cytology, uteroscopy, and 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.³³ CT or MRI of the brain can be performed if clinical signs, presentation, and symptoms suggest brain metastases.

The recommended abdominal imaging studies provide high diagnostic accuracy. Therefore, a needle biopsy is not always necessary before surgery, especially in patients and clear findings in the imaging studies. In selected individuals, needle biopsy may be considered for small lesions to establish diagnosis of RCC and guide active surveillance strategies, cryosurgery, radiofrequency, and ablation strategies.³⁴ As noted above, biopsy should also be considered if a central lesion or a homogeneous infiltration of renal parenchyma is observed on scans to rule out urothelial carcinoma or lymphoma, respectively.

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

The use of current TNM classification³⁶ and classification of histologic subtypes³⁷ are important in making treatment decisions.

Treatment of Localized Disease

Surgical resection remains an effective therapy for clinically localized RCC, with options including radical nephrectomy and nephron-sparing surgery—each detailed below. Each of these modalities is associated with

its own benefits and risks, the balance of which should optimize long-term renal function and expected cancer-free survival.

Nephron-Sparing Surgery and Radical Nephrectomy

A radical nephrectomy includes a perifascial resection of the kidney, perirenal fat, regional lymph nodes, and ipsilateral adrenal gland. Radical nephrectomy is the preferred treatment if the tumor extends into the inferior vena cava. Open, laparoscopic, or robotic surgical techniques may be used to perform radical nephrectomy. Long-term outcomes data indicate that laparoscopic and open radical nephrectomies have equivalent cancer-free survival rates.³⁸⁻⁴⁵

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.⁴⁶⁻⁵¹ Radical nephrectomy can lead to an increased risk for chronic kidney disease^{52,53} and is associated with increased risks of cardiovascular morbidity and mortality according to population-based studies.⁵⁴ When compared with radical nephrectomy, partial nephrectomy can achieve preserved renal function, decreased overall mortality, and reduced frequency of cardiovascular events.⁵⁴⁻⁵⁸

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, up to 7 cm in greatest dimension) and a normal contralateral kidney, with equivalent outcomes to radical nephrectomy.^{49,59-61} 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.⁶²

Studies with limited follow-up data show that the oncologic outcome for laparoscopic versus open nephron-sparing surgery appears to be similar.^{63,64} A study of oncologic outcomes at 7 years after surgery found metastasis-free survival to be 97.5% and 97.3% ($P = 0.47$) after laparoscopic and open nephron-sparing surgery, respectively.⁶⁵

The goals of nephron-sparing surgery should be optimal locoregional tumor control while minimizing ischemia time to ideally less than 30 minutes.⁶⁶ However, in some patients with localized RCC, nephron-sparing surgery may not be suitable because of locally advanced tumor growth or because tumor is in an unfavorable location. Laparoscopic, robotic, and open partial nephrectomy all offer comparable outcomes in the hands of skilled surgeons. Patients in satisfactory medical condition should undergo surgical excision of stage I through III tumors.

Lymph Node Dissection

Lymph node dissection has not been consistently shown to provide therapeutic benefit. The EORTC phase III trial compared radical nephrectomy with a complete lymph node dissection to radical nephrectomy alone. The results showed no significant differences in overall survival (OS), time to progression of disease, or progression-free survival (PFS) between the two study groups.⁶⁷ 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.⁶⁸ Assessment of lymph node status is based on enlargement of imaging (CT/MRI) and on assessment by direct palpation at time of surgery. CT/MRI may not detect small metastases in normal lymph nodes.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 a low RCC-specific mortality.⁷⁶ Active surveillance and ablative techniques such as cryo- or radiofrequency ablation are alternative strategies for selected patients, particularly the elderly and those with competing health risks.

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

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

Management of Stage I (T1a) Disease

The NCCN Panel prefers surgical excision by partial nephrectomy for the management of clinical stage I (T1a) renal masses. Adequate expertise and careful patient selection are important. Partial nephrectomy is most appropriate in patients with small unilateral tumors or whenever preservation of renal function is a primary issue, such as in patients having

one kidney or those with renal insufficiency, bilateral renal masses, or familial RCC. Both open and laparoscopic approaches to partial nephrectomy can be considered, depending on tumor size, location, and the surgeon's expertise.

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

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

Although distant recurrence-free survival rates of ablative techniques and conventional surgery are comparable, ablative techniques have been associated with an increased risk of local recurrence.⁷⁷⁻⁸⁰ Judicious patient selection and counseling remain of paramount importance for these less invasive technologies.

The NCCN Guidelines recommend active surveillance and ablative techniques only in selected 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.^{81,82} 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.

Management of Stage II and III Disease

The curative therapy for patients with stages II and III disease remains radical nephrectomy.⁴⁴ Radical nephrectomy is the preferred treatment for the tumors that extend into the inferior vena cava. Resection of a caval or atrial thrombus often requires the assistance of cardiovascular surgeons because treatment-related mortality may reach 10%, depending on the local extent of the primary tumor and the level of vena caval extension. Partial nephrectomy is generally not suitable for patients with locally advanced tumors; however, they may be performed in patients with locally advanced tumors if technically feasible and clinically indicated. For example, partial nephrectomy may be considered for those with small, polar, unilateral tumors.

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

Adjuvant Treatment for Clear Cell, High-Risk Localized RCC

For most patients with localized RCC, adjuvant treatment after nephrectomy has no established role in patients who have undergone a complete resection of their tumor. An exception is for patients with stage III disease, clear cell histology, and a high risk for relapse. For these patients, patients may be treated with adjuvant sunitinib (category 2B) for 1 year. There are several ongoing clinical trials testing additional targeted therapies in the adjuvant setting. Eligible patients should be offered enrollment in randomized clinical trials. Adjuvant radiation therapy after nephrectomy has not shown benefit, even in patients with nodal involvement or incomplete tumor resection.

Historically, several trials involving adjuvant therapy failed to show a reduced likelihood of relapse. Randomized trials comparing adjuvant interferon alpha (IFN- α), high-dose interleukin-2 (IL-2), or cytokine combinations with observation alone in patients who had locally advanced, completely resected RCC showed no delay in time to relapse or improvement in survival with adjuvant therapy.⁸³ A multicenter, phase III study (ASSURE; ECOG-ACRIN E2805) in patients with high-grade tumors T1b or greater found no disease-free survival (DFS) or OS benefit with use of sunitinib or sorafenib versus placebo as adjuvant therapy after nephrectomy.⁸⁴ In addition, a subgroup analysis of the ASSURE trial found that neither the prognostic category of the tumor (ie, high-risk, clear cell subset of patients) nor the dose intensity of therapy altered the lack of difference in DFS or OS reported in the original study.⁸⁵ Similarly, a primary analysis of the phase III PROTECT study for patients with high-risk, locally advanced RCC reported no significant benefit in DFS for patients treated with adjuvant pazopanib compared to placebo.⁸⁶

In contrast, the phase III S-TRAC trial was the first to show a benefit in DFS with adjuvant treatment following nephrectomy in RCC. S-TRAC was a multicenter, randomized study including 615 patients with locoregional, high-risk, clear cell cancer treated with adjuvant sunitinib (50 mg once daily; 4 weeks on, 2 weeks off) or placebo. Patients treated with sunitinib had a longer median DFS duration compared to those treated with placebo (6.8 years vs. 5.6 years; $P = .03$). Grade 3 or higher adverse events occurred in 63.4% of patients treated with sunitinib compared to 21.7% of those on placebo.⁸⁷ A subsequent subgroup analysis of patients on the S-TRAC trial found that the benefit of adjuvant sunitinib was observed across subgroups.⁸⁸ Median OS had not been reached in the sunitinib or placebo groups in either of these publications.^{87,88}

The NCCN Panel recommended including sunitinib as an option for adjuvant therapy in patients at high risk for recurrence based on the DFS

benefit demonstrated in the S-TRAC trial. Due to concerns from some panel members about toxicity, lack of a demonstrated OS benefit, and conflicting results between the ASSURE and S-TRAC trials, there was not uniform consensus that this intervention is appropriate, leading to a category 2B recommendation.

Follow-up After Treatment of Localized Disease

After surgical excision, 20% to 30% of patients with localized tumors experience relapse. Lung metastasis is the most common site of distant recurrence, occurring in 50% to 60% of patients. The median time to relapse after surgery is 1 to 2 years, with most relapses occurring within 3 years.⁸⁹

The NCCN Panel has provided a framework for follow-up of patients undergoing surveillance of a small renal mass and for patients who underwent surgery or ablative therapy of a primary RCC. The NCCN 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.⁹⁰ 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.⁹¹ 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 NCCN Panel recommends a history and physical examination, a comprehensive metabolic panel, and other tests every 6 months for 2 years and then annually for up to 5 years after diagnosis. In order to study the growth rate of the tumor, the NCCN Panel recommends abdominal imaging (with CT or MRI) within 6 months for 2 years from initiation of active surveillance; subsequent imaging (with CT, MRI, or 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.⁹² Therefore, best clinical judgment should be used in choosing the imaging modality. For patients with biopsy positive for RCC, the recommendation is to annually assess for pulmonary metastases using chest imaging techniques (chest x-ray or chest CT). The panel recommends imaging of the pelvis; CT or MRI of the head or spine, if there are neurologic symptoms; or bone scan in cases of elevated ALP, bone pain, or abnormal radiologic findings.

Follow-up After Ablative Therapy for Stage T1a

Most follow-up tests after ablative therapy included by the NCCN Panel are similar to the follow-up tests included during active surveillance. For imaging tests after ablative therapy, the NCCN Panel recommends abdominal CT or MRI with and without IV contrast unless otherwise contraindicated at 3 and 6 months to assess treatment response followed by annual abdominal CT or MRI scans for five years. The NCCN Panel recommends annual chest x-ray or CT to assess for pulmonary metastases for five years for those who have biopsy-proven low-risk RCC, non-diagnostic biopsies, or no prior biopsy to assess for liver metastases. The panel suggests repeat biopsy if there is radiographic evidence of

progressive increase in size of an ablated neoplasm with or without contrast enhancement, new nodularity in or around the treated zone, failure of the treated lesion to regress over time, or evidence of satellite or port site lesions.

Follow-up After Nephrectomy for Stages I–III

For patients with stages pT1a and pT1b after partial or radical nephrectomy, the NCCN Panel recommends a history and physical examination, comprehensive metabolic panel, and other tests every 6 months for 2 years and then annually for up to 5 years after nephrectomy. The panel recommends a baseline abdominal scan (CT, MRI, or US) for patients undergoing either partial nephrectomy or radical nephrectomy within 3 to 12 months following renal surgery. If the initial postoperative imaging is negative, abdominal imaging beyond 12 months for patients who have undergone radical nephrectomy may be performed at the discretion of the physician. For those who have undergone partial nephrectomy, abdominal scans (CT, MRI, or US) may be considered annually for 3 years based on individual risk factors. The rates of local recurrence for smaller tumors after partial nephrectomy are 1.4% to 2% versus 10% for larger tumors.^{63,93,94}

The panel recommends yearly chest imaging (chest x-ray or CT) for three years as clinically indicated thereafter and recommends imaging of the pelvis, CT or MRI of the head and spine, or bone scan performed as clinically indicated.

For patients with stage II–III after radical nephrectomy, larger tumors have a substantially higher risk of both local and metastatic recurrence; therefore, an increased frequency of examinations is recommended compared with patients with stages pT1a or pT1b. The NCCN Panel recommends a history and physical examination every 3 to 6 months for 3 years, then annually for 5 years after radical nephrectomy. The follow-up

evaluation may be extended beyond 5 years at the discretion of the physician as clinically indicated. A comprehensive metabolic panel and other tests are recommended as clinically indicated every 6 months for 2 years, then annually for 5 years after radical nephrectomy, and thereafter as clinically indicated.

The panel recommends baseline chest imaging (with CT) and abdominal scans (CT or MRI) within 3 to 6 months following surgery with continued imaging (chest CT; CT, MRI, or US of the abdomen) every 6 months for at least 3 years, and annually thereafter for up to 5 years after radical nephrectomy.⁹⁵ 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. 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 has noted that imaging beyond 5 years may be performed as clinically indicated, and site-specific imaging may be performed as symptoms warrant. Other tests such as imaging of the pelvis, CT or MRI of the head or spine, or bone scan are recommended as clinically indicated.

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 stage, grade, and ECOG performance status into low-, intermediate-, or high-risk groups for developing recurrence or metastases post-surgical treatment of localized or locally advanced RCC.⁹⁶

Management of Relapsed or Stage IV Disease

Patients with stage IV disease also may benefit from surgery. For example, lymph nodes suspicious for metastatic disease on CT may be

hyperplastic and not involved with tumor; thus, the presence of minimal regional adenopathy does not preclude surgery.

Cytoreductive nephrectomy before systemic therapy is generally recommended in 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.⁹⁷ Retrospective data from the International Metastatic RCC Database Consortium (IMDC) suggested that cytoreductive nephrectomy continues to play a role in patients treated with vascular endothelial growth factor (VEGF)-targeted agents.⁹⁸ The efficacy of newer systemic therapies is challenging the standard in some patients with metastatic disease. Recent results from the CARMENA phase III trial of patients with metastatic RCC who were eligible for cytoreductive nephrectomy found that sunitinib alone was non-inferior to sunitinib after nephrectomy.⁹⁹ The median OS was 18.4 months in the sunitinib-alone group and 13.9 months in the sunitinib after nephrectomy group (hazard ratio [HR], 0.89; 95% CI, 0.71–1.10), which did not exceed the fixed non-inferiority limit (1.20). However, many of the patients in this trial had poor-risk features, underscoring the importance of patient selection to obtain the greatest benefit from nephrectomy or targeted therapy.^{99,100} At this point in time there are no prospective data defining the role of cytoreductive nephrectomy in patients who subsequently receive checkpoint antibody therapy. Further study will better define the role of cytoreductive nephrectomy in the rapidly evolving treatment landscape for RCC.

Patients with metastatic disease who present with hematuria or other symptoms related to the primary tumor should be offered palliative nephrectomy if they are surgical candidates. In addition, the small subset of patients with potentially surgically resectable primary RCC and

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

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

Patients who have undergone a nephrectomy and years later develop an oligometastatic recurrence also have the option of metastasectomy, stereotactic body radiation therapy (SBRT),¹⁰¹⁻¹⁰³ or ablative techniques, in addition to the first-line therapy options below.

Systemic Therapy Options for Patients with Relapsed or Stage IV Disease

The cytokine era introduced IFN- α and high-dose IL-2 as therapies for RCC, which are now only used in selected patients. Targeted therapy utilizing tyrosine kinase inhibitors (TKIs), and/or anti-VEGF antibodies, is now widely used in first- and second-line treatments. Agents targeting the mammalian target of rapamycin (mTOR) are also used in this setting. 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: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus, bevacizumab in combination with interferon, cabozantinib, and lenvatinib (plus everolimus). Immune checkpoint inhibitors are the new 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. Recent studies have shown efficacy of nivolumab checkpoint monotherapy in the second-line setting for patients with advanced RCC and the combination of nivolumab and ipilimumab in the first-line setting.

Tumor histology and risk stratification of patients is important in therapy selection. The histologic diagnosis of RCC is established after surgical removal of renal tumors or after biopsy. According to WHO, the three most common histologic RCC types are clear cell RCC, papillary RCC, and chromophobe RCC.¹⁰⁴ Prognostic systems are used for risk stratification in the metastatic setting.^{105,106}

To further guide management of advanced RCC, the NCCN Kidney Cancer Panel has categorized all systemic kidney cancer therapy regimens as “preferred,” “other recommended,” or “useful under certain circumstances.” This categorization provides guidance on treatment selection by considering the efficacy, safety, evidence, and other factors that play into treatment selection. These factors include pre-existing comorbidities, nature of the disease, and in some cases consideration of access to agents. For first-line therapies, the NCCN Kidney Cancer Panel further stratified treatment preferences according to prognostic risk categories.

Prognostic Models

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

The most widely used prognostic factor model is 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 IFN.¹⁰⁵ Prognostic factors for multivariable analysis included five variables: interval from diagnosis to treatment of less than 1 year; Karnofsky performance status less than 80%; serum lactate dehydrogenase (LDH) greater than 1.5 times the upper limit of normal (ULN); corrected serum calcium greater than the ULN; 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 1 or 2 factors present are considered intermediate risk, and patients with 3 or more of the factors are considered poor risk. The MSKCC criteria have been additionally validated by an independent group at the Cleveland Clinic.¹⁰⁷

A prognostic model derived from a population of patients with metastatic RCC treated with VEGF-targeted therapy has been developed, and is known as the IMDC or Heng's model.¹⁰⁶ This model was derived from a retrospective study of 645 patients with metastatic RCC treated with sunitinib, sorafenib, or bevacizumab plus interferon. 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, Karnofsky performance status less than 80%, and time from



initial diagnosis to initiation of therapy of less than 1 year. Additional, independent, adverse prognostic factors validated in this model are absolute neutrophil count (ANC) greater than ULN and platelets greater than ULN.¹⁰⁶

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%).¹⁰⁶ This model was validated in an independent dataset.¹⁰⁸

First-line Therapy for Patients with Clear Cell RCC

Pazopanib as First-line Therapy for Clear Cell RCC

Pazopanib is an oral angiogenesis inhibitor targeting VEGF receptors (VEGFR-1, -2, and -3), platelet-derived growth factor receptors (PDGFR- α and - β), and stem cell factor receptor (c-KIT). The safety and effectiveness of pazopanib were evaluated in a phase III, open-label, international, multicenter study. Four hundred thirty-five patients with clear cell advanced RCC and measurable disease with no prior treatment or 1 prior cytokine-based treatment were randomized 2:1 to pazopanib or placebo. PFS was prolonged significantly with pazopanib in the overall study population, averaging 9.2 months versus 4.2 months for patients assigned to placebo.¹⁰⁹ The treatment-naïve subpopulation of 233 patients, randomized 2:1 to pazopanib versus placebo, had a median PFS of 11.1 months on pazopanib versus 2.8 months on placebo.¹⁰⁹ The overall response rate (ORR) was 30% with pazopanib and 3% with placebo (all results were statistically significant). Common adverse

reactions to pazopanib (any grade) included diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting, fatigue, weakness, abdominal pain, and headache. Notable grade 3 toxicity was hepatotoxicity, indicated by elevated levels of alanine (30%) and aspartate (21%) transaminase. Therefore, it is critical to monitor liver function before and during treatment with the drug.

The final analysis of OS and updated safety results of pazopanib did not show a statistically significant effect on OS.¹¹⁰ The lack of correlation between OS and PFS is attributed to the extensive crossover of placebo-treated patients to pazopanib via the parallel open-label extension, as well as other subsequent anticancer treatments that patients from both arms received after progression.¹¹⁰ In the updated analyses,¹¹⁰ no differences in the frequency or severity of adverse events or grade 3/4 adverse events were seen compared with the previous report.¹⁰⁹

Results of a large non-inferiority study (COMPARZ) of sunitinib versus pazopanib showed that these two drugs have a similar efficacy profile and a differentiated safety profile.¹¹¹ Among 1110 patients with clear cell metastatic RCC who were randomized to receive pazopanib or sunitinib, patients receiving pazopanib achieved a median PFS of 8.4 months compared with 9.5 months for patients receiving sunitinib (HR, 1.047). ORRs were 31% for pazopanib and 25% for sunitinib. Pazopanib was associated with less fatigue than sunitinib, less hand-foot syndrome, less alteration in taste, and less thrombocytopenia. However, pazopanib was associated with more transaminase elevation than sunitinib.¹¹¹ The results of the final OS analysis were similar in the two groups (HR for death with pazopanib vs. sunitinib, 0.92; 95% CI, 0.79–1.06) and for all risk subgroups.¹¹²

The results of the COMPARZ trial^{111,112} are supported by the results of another smaller phase III study (PISCES).¹¹³ The primary endpoint was



patient preference, assessed at 22 weeks. When asked about reasons for selecting one drug over another, about 70% selected pazopanib due to better quality of life (QOL), compared with 22% of the sunitinib-treated patients and the remaining 8% of patients having no preference.¹¹³

The NCCN Kidney Cancer Panel has listed pazopanib as a category 1 preferred option for first-line treatment of patients with favorable risk features with relapsed or medically unresectable clear cell stage IV RCC. Additionally, the Panel has listed pazopanib as a category 1 other recommended option for first-line treatment of patients with poor-/intermediate-risk features.

Sunitinib as First-line Therapy for Clear Cell RCC

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 (FLT-3); colony-stimulating factor (CSF-1R); and neurotrophic factor receptor (RET).^{114,115}

Preclinical data suggested that sunitinib has anti-tumor activity that may result from both inhibition of angiogenesis and inhibition of cell proliferation.^{116,117} After promising phase I and II data, the efficacy of sunitinib in previously untreated patients with metastatic RCC was studied in a large multinational phase III trial in which 750 patients with metastatic (all risk) clear cell histology RCC were randomized to receive either sunitinib or IFN- α .¹¹⁴ The patients selected for the trial had no prior treatment with systemic therapy, good performance status, and measurable disease. The median PFS was 11 months for the sunitinib arm and 5 months for the IFN- α arm. Outcomes were better for patients in the favorable risk group, but for all risk groups the patients in the sunitinib arm had longer median PFS than in the IFN- α arm. Severe adverse events (grade 3–4 toxicities) were acceptable, with neutropenia, thrombocytopenia, hyperamylasemia, diarrhea, hand-foot syndrome, and

hypertension being noteworthy in the sunitinib arm and fatigue being more common with IFN- α .

Updated results demonstrate a strong trend towards OS advantage of sunitinib over IFN- α in the first-line setting (26.4 months vs. 21.8 months, $P = .051$).¹¹⁸ The OS based on pretreatment IMDC prognostic risk was not reached for patients in the favorable risk groups, but also had a trend towards OS advantage in the sunitinib over IFN- α arm for intermediate-risk (20.7 months vs. 15.4 months) and poor-risk groups (5.3 months vs. 4 months).¹¹⁸ Results from an expanded access trial revealed that sunitinib possesses an acceptable safety profile and has activity in subgroups of patients with brain metastases, non-clear cell histology, and poor performance status.¹¹⁹ Phase II studies using modified¹²⁰ or intermittent¹²¹ sunitinib dosing schedules in patients with metastatic RCC showed high efficacy and lower toxicity.

A retrospective study using the IMDC studied the efficacy of first-line treatment with sunitinib compared with pazopanib at the population-based level. No difference in OS was seen between the two treatment options (22.3 vs. 22.6 months, respectively, $P = .65$).¹²² In addition, no difference was observed in PFS and response rates between the two treatment options.¹²²

Based on these studies and its tolerability, the NCCN Kidney Cancer Panel has also listed sunitinib as a category 1 preferred option for first-line treatment of patients with relapsed or medically unresectable clear cell stage IV RCC with good-risk features. The Panel has listed sunitinib as a category 1 other recommended option for first-line treatment of patients with relapsed or medically unresectable clear cell stage IV RCC with poor-/intermediate-risk features.

*Nivolumab and Ipilimumab in Combination as First-line Therapy for Patients with Clear Cell RCC*

Nivolumab is an antibody that selectively blocks the interaction between programmed death-1 (PD-1; expressed on activated T cells) and its ligands (expressed on antigen-presenting cells, including immune cells and tumor cells). Ipilimumab is an 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).

An open-label, multicenter, phase III trial (CheckMate 214) compared nivolumab (3 mg/kg body weight) plus ipilimumab (1 mg/kg) intravenously every 3 weeks for 4 doses followed by nivolumab monotherapy (3 mg/kg) every 2 weeks versus sunitinib monotherapy 50 mg (4 weeks on and 2 weeks off schedule) in patients with advanced RCC.¹²³ One thousand ninety-six patients were randomized (1:1) to nivolumab plus ipilimumab or sunitinib monotherapy; 425 and 422 treated patients, respectively, had intermediate or poor-risk. The co-primary endpoints for the trial included ORR, PFS, and OS in the intermediate- and poor-risk patients. The combination of nivolumab plus ipilimumab produced a higher ORR compared to sunitinib monotherapy (42% vs. 27%, $P < .001$), and a higher complete response rate (9% vs. 1%, $P < .001$) in the intermediate- and poor-risk patients. The 18-month OS rate was 75% (95% CI, 70–78) with nivolumab plus ipilimumab and 60% with sunitinib (95% CI, 55–65). The median PFS (11.6 months vs. 8.4 months; HR, .82; $P = .03$) was not statistically significant, since it didn't meet the prespecified .009 threshold.¹²³ Treatment-related adverse events were seen in 93% of patients who received nivolumab plus ipilimumab and 97% of patients who received sunitinib; grade 3 or 4 events occurred in 46% and 63% of patients, respectively. Treatment-related adverse events led to discontinuation in 22% and 12% of patients, respectively.¹²³

The data for first-line nivolumab in combination with ipilimumab for favorable-risk patients has been mixed.^{123,124} The intent-to-treat population in CheckMate 214 also included favorable-risk patients treated with nivolumab plus ipilimumab ($n = 125$) or sunitinib ($n = 124$), for a total of 550 and 546 patients, respectively.¹²³ The 18-month OS in the overall intent-to-treat population favored nivolumab plus ipilimumab versus sunitinib (78% vs. 68%), but exploratory analyses of just the favorable-risk patients favored sunitinib (88% vs. 93%). The ORR (29% and 52%; $P < .001$) and median PFS (14.3 months and 25.1 months; HR, 2.18; 99.1% CI, 1.29–3.68; $P < .001$) were also lower in favorable-risk patients taking nivolumab plus ipilimumab versus sunitinib in this study. However, the CR rates were 11% and 6% for the nivolumab plus ipilimumab combination and sunitinib arms, respectively. A separate phase I trial (CheckMate 016) supports the use of nivolumab plus ipilimumab in patients at any risk with confirmed advanced or metastatic RCC with a clear cell component, including those who received prior therapy.¹²⁴ The study included patients with poor ($n = 6$), intermediate ($n = 47$), or favorable risk ($n = 47$) according to MSKCC risk categorization. Patients with favorable risk comprised 44.7% of those taking nivolumab (3 mg/kg body weight) and ipilimumab (1 mg/kg) and 44.7% of those taking nivolumab (1 mg/kg) and ipilimumab (3 mg/kg), every 3 weeks for 4 doses, followed by nivolumab monotherapy 3 mg/kg every 2 weeks until progression or toxicity. The data for the favorable-risk patients alone was not published, but the 2-year OS for the entire cohort was 67.3% and 69.6%, respectively. The confirmed ORR for the cohort at a median follow-up time of 22.3 months was the same in both arms (40.4%).¹²⁴

Based on these data, the NCCN Kidney Cancer Panel has listed nivolumab and ipilimumab in combination as a category 1, preferred treatment option for first-line treatment for intermediate- and poor-risk patients with previously untreated, relapsed or medically unresectable, clear cell, stage IV RCC. Due to conflicting data for favorable-risk patients

in the phase III compared to the phase I trials, the NCCN Kidney Cancer Panel recommends nivolumab and ipilimumab in combination as a category 2A other recommended treatment option for first-line treatment in these patients. The FDA approval for nivolumab plus ipilimumab is narrower, only including patients with intermediate- or poor-risk RCC.

Cabozantinib as First-line Therapy for Clear Cell RCC

Cabozantinib is a small-molecule inhibitor of tyrosine kinases such as VEGFRs, MET, and AXL. An open-label, phase II trial (CABOSUN) randomized 157 patients with advanced RCC to first-line therapy with either cabozantinib (60 mg once daily) or sunitinib (50 mg once daily; 4 weeks on, 2 weeks off).¹²⁵ Patients in the CABOSUN trial were either intermediate or poor risk based on IMDC criteria. Patients treated with cabozantinib showed a significantly increased median PFS compared to those treated with sunitinib (8.2 vs. 5.6 months). Cabozantinib also showed a significantly higher ORR compared to sunitinib (46% vs. 18%). All-causality grade 3 or 4 adverse events were 67% for cabozantinib and 68% for sunitinib with diarrhea, fatigue, hypertension, palmar-plantar erythrodysesthesia, and hematologic abnormalities most commonly reported.¹²⁵

Based on these results, the NCCN Panel has included cabozantinib as a category 2A preferred first-line treatment option for poor- and intermediate-risk groups. Extrapolating on the data for poor/intermediate risk, the NCCN Kidney Cancer Panel has listed cabozantinib as a category 2B other recommended first-line treatment option for favorable-risk groups.

Active Surveillance for Select, Asymptomatic Patients with Clear Cell RCC

A subset of patients with advanced RCC show indolent progression of disease and could benefit from initial active surveillance because of the toxicity and non-curative nature of systemic therapies. A prospective

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.¹²⁶ 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 RCC can safely undergo active surveillance before starting systemic therapy. Therefore, the NCCN Panel included active surveillance as an option for select, asymptomatic patients with favorable-risk clear cell RCC.

Axitinib as First-line Therapy for Clear Cell RCC

Axitinib is a selective, second-generation inhibitor of VEGFR-1, -2, and -3.¹²⁷ As second-line therapy for patients with clear cell RCC, treatment with axitinib has clearly demonstrated greater ORR and longer median PFS compared with those treated with sorafenib. To determine whether this holds true in the first-line setting, a randomized, open-label, phase III trial was carried out in newly diagnosed patients randomized (2:1) to receive axitinib (5 mg twice daily) or sorafenib (400 mg twice daily).¹²⁸ The median PFS seen in patients treated with axitinib was 10.1 months (95% CI, 7.2–12.1) and for those treated with sorafenib was 6.5 months (95% CI, 4.7–8.3).¹²⁸ The adverse events more commonly seen with axitinib (≥10% difference) than with sorafenib treatment were diarrhea, hypertension, weight loss, decreased appetite, dysphonia, hypothyroidism, and upper abdominal pain; adverse events more commonly seen with sorafenib treatment included palmar-plantar erythrodysesthesia, rash, alopecia, and erythema.¹²⁸ The difference in PFS between patients treated with axitinib versus sorafenib is not statistically significant; however, the results demonstrated clinical activity of axitinib with acceptable toxicity profile in the first-line setting.



Another randomized, multicenter, phase II trial evaluated the efficacy and safety of axitinib dose titration in newly diagnosed patients with metastatic RCC.¹²⁹ In this study, all patients received axitinib 5 mg twice daily for 4 weeks. After this they were assigned (1:1) to placebo titration or axitinib twice-daily dose titrated stepwise to 7 mg and, if tolerated, this was titrated up to a maximum dose of 10 mg daily. More patients in the axitinib titration group achieved an objective response compared with the placebo group (54% vs. 34%).

Based on these results, the NCCN Panel has included axitinib as a first-line treatment option (category 2B) for use under certain circumstances for patients of all risk groups.

Bevacizumab Along with Interferon as First-line Therapy for Clear Cell RCC

Bevacizumab is a recombinant humanized monoclonal antibody that binds and neutralizes circulating VEGF-A. A multicenter phase III trial (AVOREN) compared bevacizumab plus IFN- α versus placebo plus IFN- α . The trial was a randomized, double-blind trial. Six hundred forty-nine patients were randomized (641 treated).¹³⁰ The addition of bevacizumab to IFN- α significantly increased PFS (10.2 vs. 5.4 months) and objective tumor response rate (30.6% vs. 12.4%). No significant increase or novel adverse effects were observed with the combination over IFN- α alone. A trend toward improved OS also was observed (23.3 months with bevacizumab plus IFN- α vs. 21.3 months for IFN- α), although the difference did not reach statistical significance.¹³⁰

In the United States, a similar trial was performed by the Cancer and Leukemia Group B (CALGB), with 732 previously untreated patients randomized 1:1 to receive either IFN- α or the combination of bevacizumab plus IFN- α . Bevacizumab plus IFN- α produced a superior PFS (8.5 months vs. 5.2 months) and higher ORR (25.5% vs. 13.1%) versus IFN- α alone. However, toxicity was greater in the combination therapy arm.¹³¹

There were no significant differences in median survival between the two groups (18.3 vs. 17.4 months for bevacizumab plus IFN- α vs. IFN- α alone).¹³²

The NCCN Kidney Cancer Panel recommends bevacizumab in combination with IFN- α as a category 1 option, useful under certain circumstances, for first-line treatment of patients of all risk groups with relapsed or medically unresectable clear cell stage IV RCC.

High-Dose IL-2 as First-line Therapy for Clear Cell RCC

IL-2–based immunotherapy is reported to achieve long-lasting complete or partial remissions in a small subset of patients. High-dose IL-2 is associated with substantial toxicity and to date attempts to characterize tumor or patient factors for best response to this therapy have been unsuccessful.¹³³⁻¹³⁵ Thus, the best criteria to select patients for IL-2 therapy are based in large part on safety and include the patient's performance status, medical comorbidities, tumor histology (clear cell), MSKCC or Survival After Nephrectomy and Immunotherapy (SANI) risk scores,^{105,136,137} and the patient's attitude toward risk.

According to the NCCN Kidney Cancer Panel, for highly selected patients with relapsed or medically unresectable stage IV clear cell RCC, high-dose IL-2 is listed as a first-line treatment option with a category 2A designation.

Temsirolimus as First-line Therapy for Clear Cell RCC

Temsirolimus is an inhibitor of the mTOR protein. mTOR regulates micronutrients, cell growth, apoptosis, and angiogenesis by its downstream effects on a variety of proteins. Efficacy and safety of temsirolimus were demonstrated at a second interim analysis of the ARCC trial, a phase III, multicenter, randomized, open-label study in previously untreated patients with advanced RCC who had 3 or more of 6



unfavorable prognostic factors.¹³⁸ The prognostic factors included: less than one year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin less than the LLN, corrected calcium greater than 10 mg/dL, LDH greater than 1.5 times the ULN, and metastasis to one or more than one organ site. Six hundred twenty-six patients were randomized equally to receive IFN- α alone, temsirolimus alone, or the combination of temsirolimus and IFN- α . Patients in both temsirolimus-containing groups were recommended pre-medication with an antihistamine to prevent infusion reactions. Patients were stratified for prior nephrectomy and geographic region. Seventy percent were younger than 65 years of age and 69% were male. The group of patients who received temsirolimus alone showed a significant improvement in OS over those receiving IFN- α alone or both drugs. The median OS was 10.9 months for patients on temsirolimus alone versus 7.3 months for those treated with IFN- α alone. The median PFS (the study's secondary endpoint) was increased from 3.1 months with IFN- α alone to 5.5 months with temsirolimus alone. The combination of temsirolimus and IFN- α not only failed to improve OS or PFS but also led to an increase in multiple adverse reactions, including grade 3 or 4 rash, stomatitis, pain, infection, peripheral edema, thrombocytopenia and neutropenia, hyperlipidemia, hypercholesterolemia, or hyperglycemia.

Based on these data, the NCCN Kidney Cancer Panel has included temsirolimus as a category 1 recommendation, useful under certain circumstances, for first-line treatment of poor-risk patients with relapsed or medically unresectable clear cell stage IV RCC.

Subsequent Therapy for Patients with Clear Cell RCC

Cabozantinib as Subsequent Therapy for Clear Cell RCC

A phase III trial (METEOR) randomized 658 patients with disease progression after previous TKI therapy to receive 60 mg/d of oral

cabozantinib (n = 331) or 10 mg/d of oral everolimus (n = 321).¹³⁹ The estimated median PFS for patients randomized to cabozantinib was 7.4 months, versus 3.8 months for everolimus (HR, 0.58; 95% CI, 0.45–0.75; $P < .001$). The ORR was 21% for cabozantinib and 5% for everolimus ($P < .001$).¹³⁹

The final analysis of the METEOR trial shows a statistically significant increase in OS in the cabozantinib arm.¹⁴⁰ A median OS of 21.4 months was shown for those treated with cabozantinib, and a median OS of 16.5 months was shown for patients treated with everolimus (HR, 0.66; 95% CI, 0.53–0.83; $P = .00026$).¹⁴⁰ A long-term follow-up analysis of the phase III METEOR trial similarly found significant improvement in median OS with cabozantinib compared to everolimus.¹⁴¹ QOL reported outcomes in the METEOR trial showed improved time to deterioration in the cabozantinib arm, but no difference compared to the everolimus arm for FSKI-19, FSKI-DRS, or EQ-5D questionnaires.¹⁴²

In a subgroup analysis of the METEOR trial involving patients with bone metastases at baseline, PFS, OS, and ORR were improved for patients treated with cabozantinib compared to everolimus. Median PFS was 7.4 months versus 2.7 months (HR, 0.33; 95% CI, 0.21–0.51), median OS was 20.1 months versus 12.1 months (HR, 0.54; 95% CI, 0.34–0.84), and ORR was 17% versus 0% for cabozantinib and everolimus, respectively.¹⁴³

The most commonly reported grade 3 or 4 treatment-related adverse effects with cabozantinib in the trial were hypertension, diarrhea, and fatigue and with everolimus were anemia, fatigue, and hyperglycemia.¹⁴⁰ The rate of treatment discontinuation due to adverse effects of the treatment was similar in both arms (9% with cabozantinib arm vs. 10% with everolimus). The longer PFS and increased OS with cabozantinib when compared to everolimus makes cabozantinib a preferred choice in



the second-line setting for advanced RCC. Based on the METEOR trial results,^{139,140} the NCCN Panel has included cabozantinib as a category 1 preferred subsequent therapy option.

A network meta-analysis comparing the relative effectiveness of treatment options for RCC after failure of first-line therapy 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.¹⁴⁴

Nivolumab as Subsequent Therapy for Clear Cell RCC

In a phase III trial (CheckMate 025), patients (N = 821) with advanced clear cell RCC, previously treated with one or more lines of therapy (excluding mTOR), were randomly assigned (in a 1:1 ratio) to receive nivolumab (3 mg/kg body weight) intravenously every 2 weeks or everolimus 10 mg/d orally.¹⁴⁵ The primary endpoint of the trial was OS. The median OS was 5.4 months longer with nivolumab compared with everolimus (25.0 vs. 19.6 months). The HR for death (from any cause) with nivolumab versus everolimus was 0.73 ($P = .002$). The ORR was also reported to be 5 times greater with nivolumab (25% vs. 5%; odds ratio, 5.98; 95% CI, 3.68–9.72; $P < .001$).¹⁴⁵ The FDA-approved dose of nivolumab is 240 mg IV every 2 weeks or 480 mg IV every 4 weeks administered over 30 minutes until disease progression or unacceptable toxicity.

Treatment-related adverse events of any grade were seen in 79% of those who received nivolumab and 88% of those who received everolimus; grade 3-4 events occurred in 19% and 37%, respectively. The most common grade 3-4 events were fatigue (2%) with nivolumab and anemia (8%) with everolimus. Toxicities led to treatment discontinuations in 8% and 13% of patients, respectively. Two deaths were reported in the

everolimus arm; there were no treatment-related deaths in the nivolumab arm.¹⁴⁵

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.¹⁴⁶

The FKSI-DRS¹⁴⁷ questionnaire was used to obtain a score for QOL of patients enrolled in the trial. The median change from baseline in the FKSI-DRS score in the nivolumab group increased over time, suggesting a significant and consistent improvement in QOL of patients in this group.¹⁴⁵ Due to the OS advantage shown by nivolumab over everolimus in the second-line setting, nivolumab is preferred over everolimus in the second-line setting for advanced RCC after an antiangiogenic agent.

Since immunotherapy response patterns differ from traditional systemic therapies, the effect of continuing treatment with nivolumab was retrospectively reviewed in patients enrolled in the CheckMate 025 trial who had disease progression on nivolumab treatment.¹⁴⁸ Results showed that nivolumab treatment beyond first progression was associated with reduced tumor burden in approximately 50% of patients with advanced RCC and 13% achieved greater than or equal to 30% reduction in tumor burden. It should be noted that patients treated with nivolumab after progression generally had more favorable disease characteristics versus those who discontinued treatment after first progression. In patients receiving nivolumab after progression, adverse events (any grade) occurred less frequently after progression versus before progression. These data suggest that a subset of patients benefit from treatment beyond progression, but this approach needs to be prospectively validated.¹⁴⁸

Based on the results of the CheckMate 025 trial¹⁴⁵ demonstrating superior OS with nivolumab compared with everolimus, the NCCN Panel has included nivolumab as a category 1 preferred subsequent therapy option.

Nivolumab and Ipilimumab in Combination as Subsequent Therapy for Clear Cell RCC

The phase I trial (CheckMate 016), mentioned above, included patients who had received one prior treatment. This trial demonstrated safety and durable response after treatment with nivolumab plus ipilimumab in patients with confirmed advanced or metastatic RCC with a clear cell component, regardless of risk.¹²⁴ Efficacy results for patients regardless of risk were stratified by treatment status; 22 patients in the nivolumab (3 mg/kg body weight) and ipilimumab (1 mg/kg) group and 26 patients in the nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) groups were previously treated. Confirmed ORR in previously treated patients was 45.5% and 38.5%, respectively.¹²⁴

Based on the above data, the NCCN Kidney Cancer Panel considers nivolumab and ipilimumab a category 2A preferred subsequent therapy option for patients with clear cell RCC.

Axitinib as Subsequent Therapy for Clear Cell RCC

A multicenter, randomized phase III study (AXIS) compared axitinib versus sorafenib as second-line therapy after 1 prior systemic therapy (with mostly cytokines or sunitinib).¹⁴⁹ The patients (n = 723) were stratified for performance status and type of prior therapy, and randomized 1:1 to axitinib (5 mg twice daily) or sorafenib (400 mg twice daily).¹⁴⁹ The overall median PFS was 6.7 months for axitinib versus 4.7 months for sorafenib (HR, 0.665; $P < .0001$), and the response rate was 19% for axitinib-versus 9% for sorafenib-treated patients ($P = .0001$). The PFS favored axitinib in both groups treated with a prior cytokine (12.1 vs. 6.5 months; $P < .0001$) and prior sunitinib (4.8 vs. 3.4 months; $P = .01$).¹⁴⁹ Adverse

events of all grades more frequent with axitinib were hypertension, fatigue, dysphonia, and hypothyroidism. Adverse events more frequent with sorafenib were hand-foot syndrome, rash, alopecia, and anemia.

The updated results of AXIS reported median OS of 20.1 months (95% CI, 16.7–23.4) with axitinib and 19.2 months (17.5–22.3) with sorafenib (HR, 0.969; 95% CI, 0.800–1.174).¹⁵⁰ Although OS did not significantly differ between the two groups, median investigator-assessed PFS was longer with axitinib; PFS was 8.3 months (95% CI, 6.7–9.2) versus 5.7 months (4.7–6.5) with sorafenib (HR, 0.656; 95% CI, 0.552–0.779).¹⁵⁰ The patient-reported outcomes were comparable for second-line axitinib and sorafenib.¹⁴⁷

In a phase II study of patients with cytokine-refractory metastatic RCC the 5-year survival rate after treatment with axitinib was 20.6% (95% CI, 10.9%–32.4%), with a median follow-up of 5.9 years.¹⁵¹ Axitinib is listed as a category 1, other recommended, subsequent therapy option by the NCCN Kidney Cancer Panel.

A *post-hoc* analysis of the AXIS trial evaluated the efficacy of axitinib and sorafenib by response to prior therapy, duration of prior therapy, and tumor burden in patients previously treated with sunitinib or cytokines.¹⁵² The analysis suggests that patients who have longer duration of response on first-line therapy have better outcomes; however, lack of response to first-line therapy does not preclude positive clinical outcomes with a second-line TKI.¹⁵²

Lenvatinib with Everolimus as Subsequent Therapy for Clear Cell RCC

Lenvatinib is a multi-targeted TKI initially developed for use in differentiated thyroid carcinoma that is refractory to standard therapy.

In a phase II trial, 153 patients with metastatic or unresectable, locally advanced, clear cell RCC who had received prior antiangiogenic therapy



were randomly assigned to lenvatinib plus everolimus or single-agent lenvatinib or single-agent everolimus.¹⁵³ The PFS was significantly prolonged with lenvatinib plus everolimus versus everolimus (median 14.6 vs. 5.5 months; HR 0.40; 95% CI, 0.24–0.68).¹⁵³ The median OS was also increased for lenvatinib plus everolimus compared with everolimus monotherapy (25.5 months vs. 15.4 months; HR, 0.67; 95% CI: 0.42–1.08).¹⁵⁴ Median OS for lenvatinib alone was 18.4 months.¹⁵⁴

Lenvatinib plus everolimus is listed as a category 1, other recommended, subsequent therapy by the NCCN Kidney Cancer Panel.

Everolimus as Subsequent Therapy for Clear Cell RCC

Everolimus (RAD001) is an orally administered inhibitor of mTOR. In the RECORD 1 trial, an international, multicenter, double-blind, randomized phase III trial, everolimus was compared with placebo for the treatment of metastatic RCC in patients whose disease had progressed on treatment with sunitinib or sorafenib.¹⁵⁵ Four hundred ten patients were randomly assigned 2:1 to receive either everolimus or placebo, and the primary endpoint was PFS. The median PFS assessed by an independent review committee was in favor of everolimus, 4.0 versus 1.9 months.¹⁵⁵ The most common adverse events reported in patients on everolimus (mostly of mild or moderate severity) versus patients in the placebo group were: stomatitis in 40% versus 8%, rash in 25% versus 4%, and fatigue in 20% versus 16%.¹⁵⁵ According to the updated results of this trial, median PFS determined by independent central review was 4.9 months for everolimus versus 1.9 months (95% CI, 1.8–1.9) for placebo.¹⁵⁶

The primary objective of the phase II (RECORD-3) study was to assess non-inferiority of first-line everolimus compared with first-line sunitinib with respect to PFS and to determine the role of first-line mTOR inhibitor in metastatic RCC.¹⁵⁷ The median PFS after first-line sunitinib was 10.71 months compared with 7.85 months for everolimus. When patients

progressed on first-line therapy, they were then crossed over to the alternative therapy and the combined PFS for the two sequences of treatment were also compared. The results indicated that the median PFS for patients treated with everolimus followed by sunitinib was 21.13 months compared with 25.79 months for those treated with sunitinib followed by everolimus (HR, 1.4; 95% CI, 1.2–1.8).¹⁵⁷ The median OS for first-line everolimus followed by sunitinib was 22.41 months compared with 32.03 months for first-line sunitinib followed by everolimus (HR, 1.2; 95% CI, 0.9–1.6).¹⁵⁷ The final OS analysis of RECORD-3 continues to support first-line sunitinib followed by everolimus (median OS was 29.5 months compared to 22.4 months for everolimus followed by sunitinib).¹⁵⁸

Everolimus is listed as a category 2A, other recommended, subsequent therapy option in the NCCN Guidelines. It is important to note that two recent randomized phase III trials (discussed in sections above) compared the efficacy of everolimus with nivolumab and cabozantinib. The results of the CheckMate 025¹⁴⁵ trial demonstrated superior OS with nivolumab compared with everolimus. The METEOR trial¹³⁹ demonstrated longer PFS and OS with cabozantinib when compared to everolimus. Based on the results of these two phase III trials, eligible patients should preferentially receive either nivolumab or cabozantinib over everolimus.

Pazopanib as Subsequent Therapy for Clear Cell RCC

The phase III trial comparing pazopanib with placebo, detailed earlier under the section titled *Pazopanib as First-line Therapy for Clear Cell RCC*, included 202 patients who received prior cytokine therapy. The average PFS in cytokine pre-treated patients was 7.4 versus 4.2 months.¹⁰⁹

A prospective phase II trial examined the activity and toxicity of second-line treatment with pazopanib (800 mg orally daily) in 56 patients with advanced metastatic RCC previously treated with a targeted agent.¹⁵⁹ The

patients enrolled in this trial had previously received first-line treatment with sunitinib (n = 39) or bevacizumab (n = 16). Responses were evaluated after 8 weeks of treatment using RECIST. The trial showed that 27% of patients (n = 15) had objective response to pazopanib; 49% (n = 27) had stable disease.¹⁵⁹ After a median follow-up of 16.7 months, the median PFS was 7.5 months (95% CI, 5.4–9.4 months).¹⁵⁹ The PFS was similar whether previous treatment was with sunitinib or bevacizumab. The estimated OS rate at 24 months was 43%.¹⁵⁹

Another retrospective analysis reported data on 93 patients with metastatic RCC treated with multiple lines of prior targeted therapies.¹⁶⁰ Among evaluable patients (n = 85) in this study, 15% (n = 13) had a partial response and the median PFS observed was 6.5 months (95% CI, 4.5–9.7).

Based on the above data, the NCCN Kidney Cancer Panel considers pazopanib a category 2A, other recommended, subsequent therapy option.

Sunitinib as Subsequent Therapy for Clear Cell RCC

Sunitinib also has demonstrated substantial anti-tumor activity in the second-line therapy of metastatic RCC after progression on cytokine therapy.^{115,161} Studies investigating the sequential use of sunitinib and sorafenib mostly are retrospective. There are prospective data, although limited, 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.¹⁶²⁻¹⁶⁶ Sunitinib is considered a category 2A, other recommended, subsequent therapy option.

Sorafenib as Subsequent Therapy for Clear Cell RCC

Sorafenib tosylate is a small molecule that inhibits multiple isoforms of the intracellular serine/threonine kinase, RAF, and also other receptor tyrosine kinases, including VEGFR-1, -2, and -3; PDGFR-β; FLT-3; c-KIT; and RET.¹⁶⁷⁻¹⁷¹

Efficacy of sorafenib was studied in patients who progressed on a prior therapy (mostly cytokines) in a phase III, placebo-controlled, randomized trial, TARGET.^{172,173} Nine hundred three patients were enrolled in this trial. The patients selected had measurable disease, clear cell histology, one prior systemic therapy in the last 8 months, an ECOG performance status of 0 to 1, and a good or intermediate prognosis. Almost all patients had undergone nephrectomy. The primary endpoint of the trial was to assess OS, and the secondary endpoint was to assess PFS.

An interim analysis conducted via independent assessment reported that sorafenib-treated patients had PFS that was significantly higher than for patients assigned to placebo (5.5 vs. 2.8 months, respectively; HR, 0.44; 95% CI, 0.35–0.55; $P = .000001$).¹⁷³ With the large difference in PFS, crossover to the sorafenib treatment arm was recommended, which likely resulted in the failure of this trial to demonstrate an OS benefit for sorafenib in the final analysis. With censoring of crossover data, treatment with sorafenib was found to be associated with an improved survival compared with placebo, 17.8 vs. 14.3 months (HR, 0.78; 95% CI, 0.62–0.97; $P = .0287$).¹⁷³ Common grade 3 to 4 adverse effects reported more in the sorafenib group than in the placebo group were hand-foot syndrome, fatigue, and hypertension.¹⁷³ This study showed the effectiveness of sorafenib was primarily in patients who progressed on prior cytokine therapy. Sorafenib has also been studied as second-line therapy in patients treated with sunitinib or bevacizumab and has been found to be safe, feasible, and effective.^{166,174}

A randomized phase II trial investigated the efficacy and safety of sorafenib versus IFN- α in previously untreated patients with clear cell RCC.¹⁷⁵ One hundred eighty-nine patients were randomized to receive continuous oral sorafenib (400 mg twice daily) or IFN- α , with an option of dose escalation of sorafenib to 600 mg twice daily or crossover from IFN- α to sorafenib (400 mg twice daily) upon disease progression. The results showed that more sorafenib-treated (68.2% vs. 39.0%) patients had tumor regression.¹⁷⁵

Sorafenib is listed as a category 2B subsequent therapy option, useful under certain circumstances.

Based on multiple alternative options and lack of current clinical use as first-line therapy among NCCN Panel Members, the NCCN Kidney Cancer Panel no longer recommends sorafenib as first-line treatment for patients with relapsed or medically unresectable stage IV clear cell RCC. Sorafenib is still widely used internationally due to its relative affordability and favorable clinical efficacy and safety for certain patient demographics (eg, Asian populations).^{176,177} Therefore, sorafenib remains an appropriate option for first-line treatment in these countries.

Other Agents as Subsequent Therapy for Clear Cell RCC

Phase II trials have shown benefit of bevacizumab monotherapy after prior treatment with a cytokine.¹⁷⁸ Bevacizumab is a category 2B subsequent therapy option for use under certain circumstances.

High-dose IL-2 as subsequent therapy is listed as a subsequent therapy option useful for selected patients with excellent performance status and normal organ function (category 2B).

A phase II trial suggested benefit to temsirolimus therapy after prior treatment with a cytokine.¹⁷⁹ A phase III trial (INTORSECT) compared the efficacy of temsirolimus to sorafenib following first-line sunitinib as a

treatment for patients with RCC.¹⁸⁰ The trial enrolled 512 patients with a performance status of 0 or 1 and either clear cell or non-clear cell histology. Patients were randomized to receive sorafenib at 400 mg twice daily or intravenous temsirolimus at 25 mg weekly. The difference in PFS, the primary endpoint of the trial, was not statistically significant ($P = .1933$) between the two arms. PFS was 4.28 months with temsirolimus compared to 3.91 months with sorafenib. A statistically significant OS advantage was observed for sorafenib. The median OS with temsirolimus was 12.27 months compared to 16.64 months with sorafenib ($P = .0144$).¹⁸⁰ However, the subgroup of individuals who had been treated with sunitinib for less than or equal to 180 days and were then treated with sorafenib did not show a survival benefit. Based on this study, in patients with a shortened response to first-line TKI, mTOR inhibition may be considered as second-line therapy.¹⁸¹ The NCCN Panel considers temsirolimus a category 2B subsequent therapy option, useful under certain circumstances.

Systemic Therapy for Patients with Non-Clear Cell RCC

Clinical trials of targeted agents have predominantly focused on patients with clear cell versus non-clear cell histology due to the high prevalence of the clear cell RCC.¹⁸² The role of targeted agents in non-clear cell RCC warrants investigation. Therefore, according to the NCCN Panel enrollment in clinical trials is the preferred strategy for non-clear cell RCC.

There are data indicating that targeted therapies approved for clear cell RCC may have benefit for non-clear cell RCC as well. In addition, there are randomized phase II studies showing activity of systemic therapy in patients with non-clear cell RCC. Systematic reviews, meta-analysis of phase II studies, and retrospective studies with targeted agents also show some activity in patients with non-clear cell RCC. Compared with responses in clear cell histologies, however, the response rates with these agents are significantly lower for non-clear cell RCC.

*Sunitinib for Non-Clear Cell RCC*

Data from expanded-access trials, phase II trials, and retrospective analyses support clinical activity of sunitinib for non-clear cell RCC.¹⁸³⁻¹⁸⁹ A phase II trial of 31 patients with non-clear cell RCC treated with sunitinib reported an ORR of 36% (95% CI, 19%–52%) and median PFS of 6.4 months (95% CI, 4.2–8.6 months).¹⁸⁶ In another study of 53 patients with non-clear RCC (papillary or chromophobe), the ORR to sunitinib or sorafenib was 23%; median PFS was 10.6 months.¹⁸⁴

Two other recent phase II studies compared treatment of sunitinib with everolimus. In the ASPEN trial, 108 previously untreated patients were randomly assigned to either everolimus or sunitinib.¹⁹⁰ Overall, median PFS, the primary endpoint of the trial, was longer in patients treated with sunitinib (8.3 vs. 5.6 months). When the results were analyzed based on risk, median PFS was longer in those treated with sunitinib (14.0 vs. 5.7 months and 6.5 vs. 4.9 months) in patients with good and intermediate risk. Patients with poor-risk features, however, did better with everolimus treatment compared with sunitinib (median, 6.1 vs. 4.0 months).¹⁹⁰ In the ESPN trial, patients with metastatic non-clear cell RCC were randomized to treatment with everolimus or sunitinib.¹⁹¹ In an interim analysis of 68 patients, first-line therapy with sunitinib resulted in median PFS of 6.1 months versus 4.1 months with first-line everolimus ($P = .6$). There was no statistically significant difference observed in final OS between the two treatment arms (16.2 for first-line sunitinib vs. 14.9 months with everolimus, $P = .18$).¹⁹¹ In patients with tumors with *no* sarcomatoid features ($n = 49$), the median OS was 31.6 months with sunitinib and 10.5 months with everolimus ($P = .075$).

A meta-analysis of randomized clinical trials for patients with non-clear cell RCC found that treatment with TKIs reduced the risk of progression compared with mTOR inhibitors.¹⁹² The study found sunitinib reduced the risk of progression compared to everolimus in the first-line setting (HR

0.67; 95% CI, 0.56–0.80; $P < .00001$). However, no significant differences between TKIs and mTOR inhibitors were found for OS and ORR.

Sunitinib is listed as a category 2A preferred option for treatment-naïve patients with stage IV non-clear cell RCC.

Cabozantinib for Non-Clear Cell RCC

While no prospective trials have been done for cabozantinib in patients with non-clear cell RCC, a few retrospective studies^{193,194} and real-world data reports¹⁹⁵ support its use as systemic therapy in this population. A retrospective study of 30 patients with non-clear cell RCC found clinical benefit for patients treated with cabozantinib.¹⁹³ The median PFS was 8.6 months and median OS was 25.4 months. The ORR was 14.3% among the 28 patients with measurable disease. The NCCN Panel included cabozantinib as a category 2A, other recommended option for patients with relapsed or stage IV, non-clear cell RCC.

Everolimus for Non-Clear Cell RCC

The data on the benefit of everolimus in patients with non-clear cell RCC are limited. Data from subgroup analyses of an expanded-access trial and case reports support clinical use of everolimus in patients with non-clear cell RCC.¹⁹⁶⁻¹⁹⁸

The efficacy and safety of everolimus in patients with metastatic RCC of non-clear cell histology were evaluated in a subgroup of patients ($n = 75$) enrolled in the RAD001 Expanded Access Clinical Trial in RCC (REACT).¹⁹⁶ Median duration of treatment with everolimus was similar in the non-clear cell subgroup and in the overall REACT trial population (12.14 weeks vs. 14.0 weeks, respectively). The ORR (1.3% vs. 1.7%) and rate of stable disease (49.3% vs. 51.6%) were similar as well, suggesting similar efficacy in clear and non-clear cell RCC.¹⁹⁶ The most commonly reported Grade 3 and 4 adverse events, respectively, in the

non-clear cell RCC subgroup included: anemia (9.3% and 8.0%), pleural effusion (9.3% and 0%), dyspnea (8.0% and 2.7%), fatigue (8.0% and 0%), asthenia (4.0% and 1.3%), stomatitis (4.0% and 0%), and pneumonitis (4.0% and 0%).¹⁹⁶

In a phase II study, 49 patients with non-clear cell RCC previously treated with sunitinib or sorafenib were given everolimus 10 mg orally daily until disease progression or unacceptable toxicity.¹⁹⁸ The histology of the enrolled patients included papillary (n = 29), chromophobe (n = 8), collecting duct (n = 2), sarcomatoid (n = 4), and unclassified (n = 6). The median PFS was 5.2 months. The ORR was 10.2% with all of the responses being partial. Twenty-five patients (51%) had stable disease; 16 patients (32.7%) progressed despite everolimus. Adverse events reported in the trial, greater than Grade 3, included anemia (10.2%), hyperglycemia (8.2%), infection (6.1%), and pneumonitis (4.1%).¹⁹⁸

Final results from a phase II trial (RAPTOR) suggest that everolimus (10 mg once daily) provides an anti-tumor effect in previously untreated patients with advanced papillary RCC.¹⁹⁹ The median PFS for type 1 and type 2 histology was 7.9 months (95% CI, 2.1–11.0) and 5.1 months (95% CI, 3.3–5.5), respectively. Median OS was 28.0 months (95% CI, 7.6–not estimable) for type 1 and 24.2 months (95% CI, 15.8–32.8) for type 2 histology. Common adverse events grade 2 or greater included asthenia, anemia, and fatigue.¹⁹⁹

Based on these trials, the NCCN Panel has included everolimus as a category 2A, other recommended option for patients with non-clear cell RCC.

The NCCN Panel also lists lenvatinib plus everolimus as a category 2A, useful under certain circumstances, treatment option for patients with non-clear cell RCC.

Pazopanib and Axitinib for Non-Clear Cell RCC

The clinical benefit of pazopanib or axitinib has not yet been established in patients with non-clear RCC. There is an ongoing clinical trial evaluating the efficacy of pazopanib in patients with non-clear cell RCC in the second-line setting.²⁰⁰ Two phase II trials with pazopanib or axitinib had promising efficacy and tolerable toxicity.^{201,202} A phase II trial of pazopanib in 28 evaluable patients in Korea with locally advanced or metastatic non-clear cell RCC, excluding collecting duct or sarcomatoid type, had promising efficacy: 8 patients achieved a confirmed partial response with ORR of 28%.²⁰¹ A phase II trial of axitinib in 40 patients with recurrent or metastatic non-clear cell RCC who had failed treatment with temsirolimus found a median PFS of 7.4 months and ORR of 37.5%.²⁰² A retrospective analysis of an Italian multicenter cohort of non-clear cell RCC patients found treatment with pazopanib to be effective and safe.²⁰³

Based on extrapolation, the NCCN Kidney Cancer Panel has included these therapies as a therapy option for patients with relapsed or medically unresectable stage IV disease with non-clear cell histology (category 2A) for use under certain circumstances.

Bevacizumab Monotherapy for Non-Clear Cell RCC

A small phase II trial studied bevacizumab monotherapy in patients with papillary RCC. This study closed early due to a very small and slow accrual of 5 patients; 3 patients had undergone a prior nephrectomy, 1 patient had resection of a liver metastasis, and 1 patient had received prior temsirolimus. The PFS reported for each of these patients was 25, 15, 11, 10, and 6 months. Main toxicities reported were grade 1–2 toxicities, such as hypertension, creatinine elevations, and proteinuria.²⁰⁴ The NCCN Panel has included bevacizumab as a therapeutic option for patients with non-clear cell RCC (category 2A).

*Erlotinib for Non-Clear Cell RCC*

The efficacy of erlotinib, an oral epidermal growth factor receptor (EGFR) TKI, was studied in patients with advanced papillary RCC.²⁰⁵ Fifty-two patients were treated with erlotinib given orally once daily. The ORR was 11% (5 of 45 patients; 95% CI, 3%–24%), and the disease control rate (defined as stable disease for 6 weeks, or confirmed partial response or complete response using RECIST) was 64%. The median OS was 27 months.²⁰⁵ This study demonstrated disease control and survival outcomes of interest with an expected toxicity profile with single-agent erlotinib.

The NCCN Kidney Cancer Panel has included erlotinib as a category 2A option, useful under certain circumstances, for first-line therapy for patients with relapsed or medically unresectable stage IV non-clear cell RCC.

Nivolumab for Non-Clear Cell RCC

A retrospective analysis evaluated the response to at least one dose of nivolumab in patients with metastatic, non-clear cell RCC.²⁰⁶ This study evaluated 35 patients for response and found 20% had partial response and 29% had stable disease, with a median follow-up of 8.5 months and median PFS of 3.5 months. Treatment-related adverse events of any grade were noted in 37% of patients, most commonly: fatigue, fever, and rash.

A separate retrospective analysis found modest responses with PD-1/PD-L1 inhibitors in 43 patients also with metastatic, non-clear cell RCC.²⁰⁷ An objective response was achieved in 8 patients (19%), including 4 patients (13%) that received PD-1/PD-L1 monotherapy.

The NCCN Panel recommends nivolumab as a category 2A option for select patients with advanced RCC with non-clear cell histology.

Bevacizumab + Erlotinib for Advanced Papillary RCC Including Hereditary Leiomyomatosis and RCC

Hereditary leiomyomatosis and 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.²⁰⁸ 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 41 patients with advanced papillary RCC (HLRCC-associated RCC; n = 20 or sporadic papillary RCC; n = 21) treated with bevacizumab plus erlotinib.²⁰⁹ Nineteen patients in this study had received at least one prior line of therapy. The ORR was 60% for those with HLRCC compared to 29% with sporadic papillary RCC. Median PFS was 24.2 months in the HLRCC group compared to 7.4 months in the sporadic papillary RCC group. Most adverse events were grades 1 or 2, with the most frequent grade 3 and 4 adverse events being hypertension (24.3%) and proteinuria (12%). One patient died of gastrointestinal hemorrhage, possibly related to treatment with bevacizumab.²⁰⁹

Based on these results, the NCCN Panel recommends bevacizumab plus erlotinib for select patients with advanced RCC and papillary histology, including HLRCC (category 2A).

Bevacizumab + Everolimus for Advanced Non-Clear Cell RCC

A phase II trial of treatment-naïve patients with metastatic non-clear cell RCC studied the efficacy and safety of treatment with bevacizumab plus everolimus.²¹⁰ For the 34 evaluable patients, median PFS, OS, and ORR were 11.0 months, 18.5 months, and 29%. Patients with tumors that contained significant papillary or chromophobe elements showed higher PFS and ORR than other histologies ($P < .001$). The most common grade

3 or higher adverse events were hyperglycemia (11%), hypertriglyceridemia (14%), lymphopenia (20%), hypertension (29%), and proteinuria (18%).²⁰³

Based on these results, the NCCN Panel recommends bevacizumab plus everolimus (category 2A) for select patients with advanced RCC with non-clear cell histology.

Temsirolimus for Non-Clear Cell RCC

A retrospective subset analysis of the global ARCC trial demonstrated benefit of temsirolimus not only in clear cell RCC but also in non-clear cell histology.^{138,211} In patients with non-clear cell RCC (predominantly papillary RCC), the median OS was 11.6 months with temsirolimus and 4.3 months with IFN- α . This is the only reported phase III trial that included patients with RCC with non-clear cell histologies.

Randomized clinical trials in rarer subgroups of patients are often challenging. Consistent with the results of this phase III 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.²¹²

Temsirolimus is a category 1 recommendation for non-clear cell RCC patients with poor prognosis features (according to MSKCC risk criteria) and is a category 2A recommendation for patients belonging to other prognostic non-clear cell risk groups. The panel has categorized temsirolimus as a regimen useful under certain circumstances for patients with non-clear cell histology regardless of risk group.

Chemotherapy for Metastatic RCC

Treatment of RCC with sarcomatoid features and non-clear cell histologies remains a challenge. Sarcomatoid variant is an aggressive form of RCC that can occur in any histologic subtype.²¹³ Sarcomatoid RCC is

associated with a poor prognosis.²¹⁴⁻²¹⁸ Chemotherapy plays a role in the management of a variety of sarcomas; therefore, its use in sarcomatoid RCC patients has been explored. Gemcitabine in combination with doxorubicin or in combination with capecitabine has shown some activity in patients with non-clear cell or clear cell tumors with sarcomatoid features.²¹⁹⁻²²⁴ The potential role of sunitinib in combination with gemcitabine has been investigated in a phase II trial of RCC with sarcomatoid features.²²⁵ The role of bevacizumab in combination with capecitabine and gemcitabine has been studied in a phase II trial of sarcomatoid RCC with low response rates.²²⁶ The results show that the combination was well tolerated and is active, especially in patients with rapidly progressing disease.²²⁵ There are ongoing trials studying sunitinib in combination with gemcitabine compared to sunitinib alone in patients with sarcomatoid features.²²⁷

Among the non-clear cell histologies, renal medullary carcinoma is extremely rare, comprising approximately 2% of all primary renal tumors in young people.^{228,229} Metastatic disease is seen at presentation in 67% to 95% of patients.²²⁸⁻²³⁰ Chemotherapy remains the focus of treatment for this subtype, although the prognosis remains dismal.

Collecting-duct carcinoma is also a very rare type of non-clear cell RCC, 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.²³¹⁻²³⁴ 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.²³⁵ The results showed a response rate of 26% and an OS of 10.5 months.²³⁵



The NCCN Kidney Cancer Panel has noted in a footnote that chemotherapy is an option for treatment of clear cell and non-clear cell RCC with predominant sarcomatoid features. The chemotherapy regimens that have shown some benefit for patients with predominant sarcomatoid features include: gemcitabine in combination with doxorubicin or sunitinib (both category 2B). In addition, the panel has noted that in patients with other non-clear cell subtypes such as collecting duct or medullary subtypes, partial responses to cytotoxic chemotherapy have been observed (gemcitabine in combination with carboplatin or cisplatin; or paclitaxel with carboplatin) and other platinum-based chemotherapies currently used for urothelial carcinomas.

Sorafenib is No Longer Recommended for Non-Clear Cell RCC

Phase II trials and retrospective analyses support clinical activity of sorafenib^{236,237} in patients with non-clear cell histologies. Similar to sunitinib, the data indicate that compared with clear cell type RCC, clinical activity of these drugs expressed seems to be reduced in patients with non-clear cell histologies. In another study of 53 patients with non-clear RCC (papillary or chromophobe), the ORR to sunitinib or sorafenib was 23%; median PFS was 10.6 months.¹⁸⁴

The NCCN Panel does not recommend sorafenib use for patients with stage IV non-clear cell RCC.

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

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

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

Supportive Care

Supportive care remains a mainstay of therapy for *all* patients with metastatic RCC (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.²³⁸

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.²³⁹⁻
²⁴¹ 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.^{242,243}



The role of bone-modifying agents such as bisphosphonates (eg, zoledronic acid) has been well established in this setting.^{244,245} 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.²⁴⁶ 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; $P = .0007$).²⁴⁶

The NCCN Kidney Cancer 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](#)).



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Discussion
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