National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Kidney Cancer

Version 2.2017 — October 31, 2016

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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/physician.html.

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

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 2.2017 Updates
Kidney Cancer

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Discussion

Updates in Version 2.2017 of the NCCN Guidelines for Kidney Cancer from from Version 1.2017 include:

MS-1

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

Updates in Version 1.2017 of the NCCN Guidelines for Kidney Cancer from Version 3.2016 include:

KID-1

- Initial workup
  - 4th bullet was revised by adding " ±" to "Abdominal ± pelvic CT"
  - 5th bullet, chest imaging was clarified as "chest x-ray" and "Chest CT" was added to the "If clinically indicated" bullet.
  - Footnote "a" was added, "Imaging with contrast when clinically indicated." Also added to all KID-B pages.
- Primary treatment
  - For Stage I (pT1a), the option for ablative techniques was revised: "Ablative techniques *in selected patients* ~~for non-surgical candidates~~"
  - For Stage II, III, "Partial nephrectomy, if clinically indicated" was added.

KID-2

- Stage IV
  - Primary treatment for potentially surgically resectable primary with multiple metastatic sites was revised: "Cytoreductive nephrectomy in select patients ~~prior to systemic therapy~~."
  - For surgically unresectable, "tissue sampling" was added before first-line therapy.

KID-3

- Predominant clear cell histology
  - First-line therapy
    - ◊ The first-line therapy options were reorganized and "alphabetical by category and preference" was added to the heading.
    - ◊ "Preferred" was added to both sunitinib and pazopanib.
  - Subsequent therapy
    - ◊ The subsequent therapy options were reorganized by removing the "After antiangiogenic therapy" and "after cytokine therapy" categories and adding "Alphabetical by category and preference" to the heading.
    - ◊ "Preferred" was added to cabozantinib (category 1) and nivolumab (category 1)

KID-3 (continued)

- Subsequent Therapy
  - ◊ The category designation for the following options were revised:
    - – Lenvatinib + everolimus was changed from a category 2A to category 1 designation.
    - – Everolimus was category 1 after antiangiogenic therapy and after cytokine therapy and is now a category 2A.
    - – Pazopanib was category 2A after antiangiogenic therapy and a category 1 after cytokine therapy and is now a category 2A.
    - – Sorafenib was category 2A after antiangiogenic therapy and a category 1 after cytokine therapy and is now a category 2A.
    - – Sunitinib was category 2A after antiangiogenic therapy and a category 1 after cytokine therapy and is now a category 2A.
  - The following footnotes were removed from this page:
    - ◊ "Category 1 recommendations are listed in order of FDA approval."
    - ◊ "Currently available tyrosine kinase inhibitors used in first-line therapy include: axitinib, pazopanib, sorafenib, or sunitinib."

KID-4

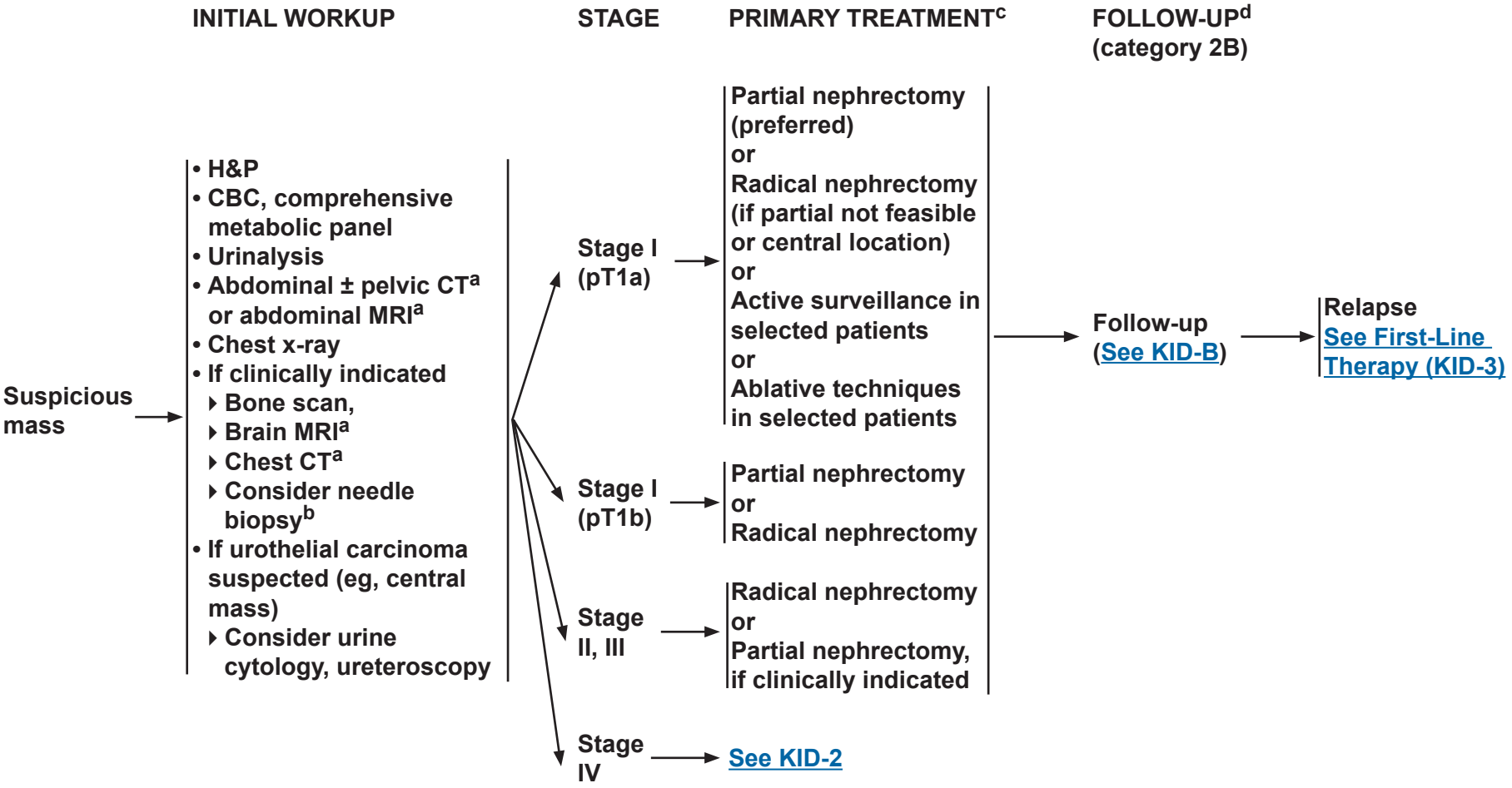
- Non-clear cell histology
  - ◊ The systemic therapy options were reorganized and "alphabetical by category and preference" was added to the heading.
  - ◊ "Preferred" was added to sunitinib
  - ◊ Cabozantinib was added with a category 2A designation.
  - ◊ Lenvatinib + everolimus was added with a category 2A designation.
  - ◊ Nivolumab was added with a category 2A designation.

KID-A

- Principles of surgery
  - 1st bullet, 1st sub-bullet was revised from "Small unilateral tumors (Patients with T1a and selected T1b and T2a tumors)" to "Unilateral Stage I-III tumors where technically feasible."
  - 6th bullet, 1st sub-bullet was revised, "Can be considered for *selected* patients with clinical stage T1 renal lesions ~~who are not surgical candidates~~."

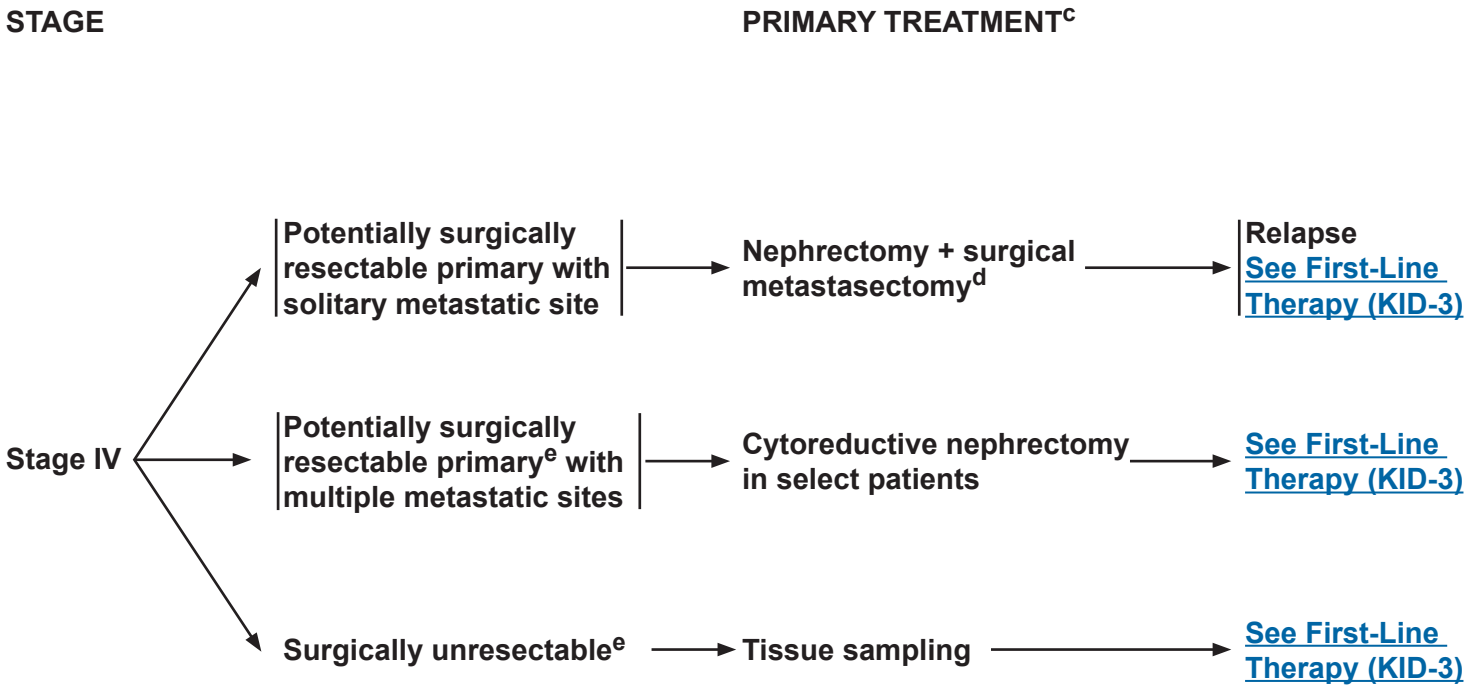
KID-B 1 of 4

- Follow-up
  - Bullet regarding pelvic imaging was revised, "Pelvic ~~imaging~~ *CT or MRI*, as clinically indicated"



[a]Imaging with contrast when clinically indicated.
[b]Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance, cryosurgery, and radiofrequency ablation strategies.
[c]See Principles of Surgery (KID-A).
[d]No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

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



[c] See Principles of Surgery (KID-A).
[d] No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.
[e] Individualize treatment based on symptoms and extent of metastatic disease.

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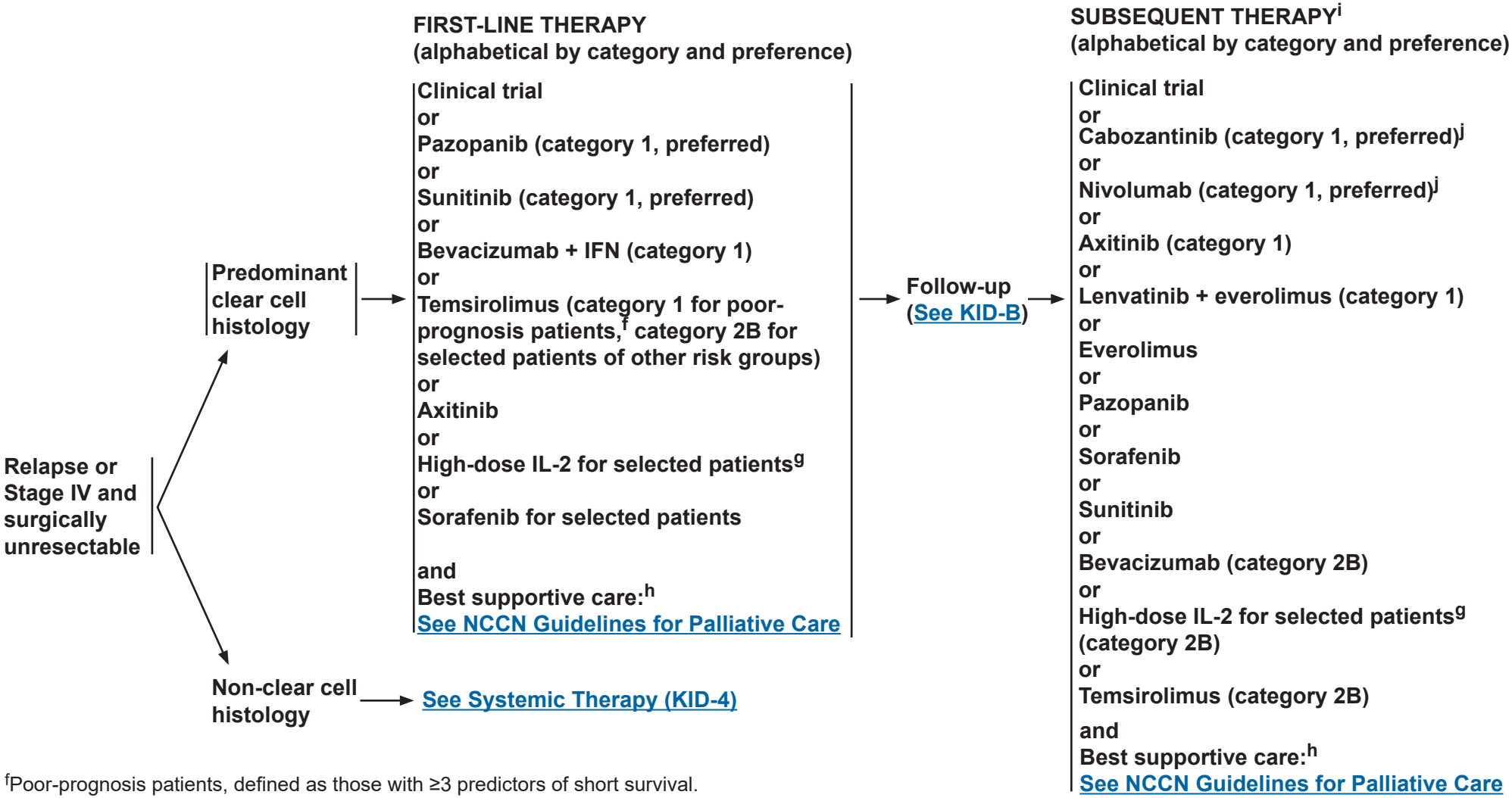
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[f]Poor-prognosis patients, defined as those with ≥3 predictors of short survival. See Predictors of Short Survival Used to Select Patients for Temsirolimus (KID-C).

[g]Patients with excellent performance status and normal organ function.

[h]Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.

[i]In clear cell and non-clear cell RCC with predominant sarcomatoid features, gemcitabine + doxorubicin (category 2B) and gemcitabine + sunitinib (category 2B) have shown benefit.

[j]Based on the results of phase III trials, eligible patients should preferentially receive this agent over everolimus. See Discussion.

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Relapse or Stage IV and surgically unresectable → **Non-clear cell histology** →

SYSTEMIC THERAPY[i,k]
(alphabetical by category and preference)

Clinical trial (preferred)
or
Sunitinib (preferred)
or
Axitinib
or
Bevacizumab
or
Cabozantinib
or
Erlotinib
or
Everolimus
or
Lenvatinib + everolimus
or
Nivolumab
or
Pazopanib
or
Sorafenib
or
Temsirolimus (category 1 for poor-prognosis patients;[f] category 2A for other risk groups)

and
Best supportive care:[h] See NCCN Guidelines for Palliative Care

→ **Follow-up (See KID-B)**

[f]Poor-prognosis patients, defined as those with ≥3 predictors of short survival. See Predictors of Short Survival Used to Select Patients for Temsirolimus (KID-C).
[h]Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.
[i]In clear cell and non-clear cell RCC with predominant sarcomatoid features, gemcitabine + doxorubicin (category 2B) and gemcitabine + sunitinib (category 2B) have shown benefit.
[k]Partial responses have been observed for cytotoxic chemotherapy (carboplatin + gemcitabine, carboplatin + paclitaxel, or cisplatin + gemcitabine) with collecting duct or medullary subtypes.

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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**

- **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 may be required for extensive inferior vena cava involvement.**

- **Observation or ablative techniques (eg, cryosurgery, radiofrequency ablation):**
  - **Can be considered for selected patients with clinical stage T1 renal lesions.**
  - **Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance, cryosurgery, and radiofrequency ablation strategies.**
  - **Randomized phase III comparison with surgical resection (ie, radical or partial nephrectomy by open or laparoscopic techniques) has not been done.**
  - **Ablative techniques are associated with a higher local recurrence rate than conventional surgery.[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**

[a]Campbell SC, Novick AC, Belldegrun A, et al. Practice Guidelines Committee of the American Urological Association. Guideline for management of the clinical T1 renal mass. J Urol 2009;182:1271-1279.
[b]Kunkle DA, Uzzo RG. Cryoablation or radiofrequency ablation of the small renal mass: A meta-analysis. Cancer 2008;113:2671-2680.

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

Stage I (pT1a)

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**

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[a]Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.
[b]No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years at the discretion of the physician. Further study is required to define optimal follow-up duration.
[c]Imaging with contrast when clinically indicated.

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

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[a]Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.
[b]No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years at the discretion of the physician. Further study is required to define optimal follow-up duration.
[c]Imaging with contrast when clinically indicated.

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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 or chest x-ray) 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**

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[a]Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.
[b]No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years at the discretion of the physician. Further study is required to define optimal follow-up duration.
[c]Imaging with contrast when clinically indicated.

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FOLLOW-UP[d] (category 2B)

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

- 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

[c]Imaging with contrast when clinically indicated.
[d]No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on treatment schedules, side effects, comorbidities, and symptoms.

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PREDICTORS OF SHORT SURVIVAL USED TO SELECT PATIENTS FOR TEMSIROLIMUS[a]

Poor-prognosis patients are defined as those with ≥3 predictors of short survival.

- **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**

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

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Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging System for Kidney Cancer (7th ed., 2010)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney
T2b	Tumor more than 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 grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly 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)

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	N0 or N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit **www.springer.com**.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

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Discussion

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 noted.

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Overview

An estimated 62,700 Americans will be diagnosed with renal cancer and 14,240 will die of the disease in the United States in 2016.[1] Renal cell carcinoma (RCC) comprises approximately 3.8% of all new cancers, with a median age at diagnosis of 64 years. Approximately 90% of renal tumors are RCC, and approximately 80% of these are clear cell tumors.[2,3] Other less common cell types include papillary, chromophobe, translocation, and Bellini duct (collecting duct) tumors. Medullary renal carcinoma is a variant of collecting duct renal carcinoma and was described initially as occurring in patients who are sickle-cell trait positive.

Smoking and obesity 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.[4,5] Analysis of the SEER database indicates that renal cell cancer incidence has been rising on average 1.1% each year and death rates have been falling on average 0.7% each year from 2004 through 2013.[6] The 5-year survival for localized cancer has increased from 88.4% (during 1992–1995) to 92.5% (during 2006–2012) and for advanced disease from 7.3% (during 1992–1995) to 11.6% (during 2006–2012).[7] 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.[8-17] RCC primarily metastasizes to the lung, lymph nodes, bone, liver, adrenal gland, and brain.[5]

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 between 07/15/15 and 07/15/16, using the following search terms: Renal Cell Carcinoma or Kidney Cancer. An update search was carried out before the publication of this document. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[18]

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 (eg, 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 on the NCCN website.

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[19,20] 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,[21] 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.[22] For metastatic evaluation, at the very least, chest radiography must be performed, although chest CT is more accurate than chest radiograph for chest staging.[23-25]

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.[26,27] All imagining studies may be performed with contrast, if indicated.

A central renal mass may suggest the presence of urothelial carcinoma; if so, urine cytology, uteroscopy, and biopsy should be considered.

Most bone and brain metastases are symptomatic at diagnosis. Therefore, a bone scan is not routinely performed unless the patient has an elevated serum alkaline phosphatase (ALP) or complains of bone pain.[28] 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.[29] 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.[30]

The use of current TNM classification[31] and classification of histologic subtypes[32] 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.[33-40]

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.[41-46] Radical nephrectomy can lead to an increased risk for chronic kidney disease[47,48] and is associated with increased risks of cardiovascular morbidity and mortality according to population-based studies.[49] When compared with radical nephrectomy, partial nephrectomy can achieve preserved renal function, decreased overall mortality, and reduced frequency of cardiovascular events.[49-53] 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.[44,54-56] 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.[57]

Studies with limited follow-up data show that the oncologic outcome for laparoscopic versus open nephron-sparing surgery appears to be similar.[58,59] 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.[60]

The goals of nephron-sparing surgery should be optimal locoregional tumor control while minimizing ischemia time to ideally less than 30 minutes.[61] 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.[62] 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.[63] Assessment of lymph nodes 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.[64]

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.[65-67] Adrenalectomy is not indicated when imaging shows a normal adrenal gland or if the tumor is not high-risk, based on size and location.[68]

Active Surveillance and Ablative Techniques

Active surveillance[69,70] 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 and other comorbidities often have a low RCC-specific mortality.[71] 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 (pT1a and pT1b), stage II, and stage III.

Management of Stage I (pT1a) Disease

The NCCN Panel prefers surgical excision by partial nephrectomy for the management of clinical stage I (pT1a) 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 (pT1a) 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.[69]

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.[72-75] 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 (pT1b) Disease

Partial nephrectomy for localized RCC has an oncologic outcome similar to that of radical surgery for T1b tumors.[76,77] 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.[39] 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.

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.[78]

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 re-iterated 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.[79] The analysis suggests that continued follow-up/surveillance after 5 years may be of potential value in some patients. 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 pT1a

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.[80] 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 pT1a

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 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

Adjuvant treatment after nephrectomy currently has no established role in patients who have undergone a complete resection of their tumor. No systemic therapy has yet been shown to reduce the 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.[81] A recently reported multicenter, phase III study (ECOG-ACRIN E2805) in patients with high-grade tumors T1b or greater found no survival benefit with use of sunitinib or sorafenib versus placebo as adjuvant therapy after nephrectomy.[82] Observation remains the standard of care after nephrectomy, and eligible patients should be offered enrollment in randomized clinical trials. There are several ongoing clinical trials and recently completed trials that explore the role of targeted therapy in the adjuvant setting. Adjuvant radiation therapy after nephrectomy has not shown benefit, even in patients with nodal involvement or incomplete tumor resection. For patients with stages pT1a and pT1b after partial or radical nephrectomy, the NCCN Panel recommends history and physical examination and 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, and 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.[83-85]

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 or chest x-ray; CT, MRI, or US of the abdomen) every six months for at least three years, and annually thereafter for up to 5 years after radical nephrectomy.[86] While the use of US imaging for follow-up is an option for low-risk patients, CT is the preferred modality for those with 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).[87] 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.[87]

Management of Advanced 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. In addition, the small subset of patients with potentially surgically resectable primary RCC and a solitary resectable metastatic site are candidates for nephrectomy and surgical metastasectomy. Candidates include patients who: 1) initially present with primary RCC and a solitary site of metastasis; or 2) develop a solitary recurrence after a prolonged disease-free interval from nephrectomy. Sites of solitary metastases that are amenable to this approach include the lung, bone, and brain. The primary tumor and the metastasis may be resected during the same operation or at different times. Most patients who undergo resection of a solitary metastasis experience recurrence, but long-term PFS has been reported in these patients.

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.[88] 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.[89]

A prognostic model derived from a population of patients with metastatic RCC treated with vascular endothelial growth factor (VEGF)-targeted therapy has been developed, and is known as the International Metastatic RCC Database Consortium or Heng's model.[90] 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 greater than ULN and platelets greater than ULN.[90]

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%).[90] This model was recently validated in an independent dataset.[91]

Primary Treatment of Relapsed or Stage IV Disease and Surgically Unresectable Disease

Cytoreductive nephrectomy before systemic therapy is generally recommended in patients with a potentially surgically resectable primary tumor mass. Randomized trials showed a benefit of cytoreductive nephrectomy in patients who received IFN-α therapy after surgery. In similar phase III trials, the SWOG and the EORTC randomized patients with metastatic disease to undergo either nephrectomy followed by IFN-α therapy or treatment with IFN-α alone.[92-94] A combined analysis of these trials showed that median survival favored the surgery plus IFN-α group (13.6 vs. 7.8 months for IFN-α alone).[92-95]

Patient selection is important to identify those who might benefit from cytoreductive therapy. Patients most likely to benefit from cytoreductive nephrectomy before systemic therapy are those with lung-only metastases, good prognostic features, and good performance status.[96] While similar data are not available for patients who are candidates for high-dose IL-2 (see below), data from the UCLA renal cancer database and from a variety of publications by other groups suggest that nephrectomy also provides benefit to patients who undergo other forms of immunotherapy.[97] As for the role of nephrectomy for patients presenting with metastatic disease and considered for targeted therapies (detailed below), randomized trials are ongoing at this time, but data from the International Metastatic RCC Database Consortium suggest that cytoreductive nephrectomy continues to play a role in patients treated with VEGF-targeted agents.[98] 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 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.

First-line Therapy for Patients with Predominantly Clear Cell Carcinoma

Cytokine Therapy

Until late 2005, systemic treatment options for metastatic RCC were limited to cytokine therapy and clinical trials of novel agents. For patients with metastatic, recurrent, or unresectable clear cell RCC various combinations and dosages of IL-2 and IFN were studied in randomized trials. IL-2 was shown to have potent antitumor activity first in several murine tumor models[99] and subsequently in patients with RCC.[100-102] With both IFN-α and IL-2, objective response rates of 5% to 27% have been reported.[102-104] Although these agents have been helpful for some patients, in most cases the clinical benefit is modest at best and is achieved at the expense of significant toxicity.

High-dose IL-2 as First-line Therapy for Predominantly Clear Cell Carcinoma

IL-2-based immunotherapy is reported to achieve long-lasting complete or partial remissions in a small subset of patients. In patients treated with IFN-α, durable complete responses are rare. While direct comparison of IFN-α and high-dose intravenous bolus IL-2 as approved by the FDA and used in U.S. centers has not been performed, data from a French multicenter study suggested similar outcomes from IFN-α or infusional IL-2, with superior responses at the cost of higher toxicity reported in the combination therapy group. 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.[99,103,105] 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 (predominantly clear cell), MSKCC or Survival After Nephrectomy and Immunotherapy (SANI) risk scores, [88,97,106] 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 renal carcinoma, high-dose IL-2 is listed as a first-line treatment option with a category 2A designation.

Targeted Therapy

Targeted therapy utilizing tyrosine kinase inhibitors (TKIs) and anti-VEGF antibodies is widely used in first- and second-line treatments. To date, seven such agents have been approved by the FDA for the treatment of advanced RCC: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus, and bevacizumab in combination with interferon.

Tumor histology and risk stratification of patients is important in targeted therapy selection. The histologic diagnosis of RCC is established after surgical removal of renal tumors or after biopsy. According to the WHO, the three most common histologic RCC types are clear cell RCC, papillary RCC, and chromophobe RCC.[107] Prognostic systems are used for risk stratification in the metastatic setting.[88,90]

Pazopanib as First-line Therapy for Predominantly Clear Cell Carcinoma

Pazopanib is an oral angiogenesis inhibitor targeting VEGFR-1, -2, and -3, PDGFR-α and -β, and c-KIT. The safety and effectiveness of pazopanib was 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.[108] The treatment-naive 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.[108] The objective response rate was 30% with pazopanib and 3% with placebo (all results were statistically significant). Common adverse reactions to pazopanib (any grade) included diarrhea (52%), hypertension (40%), hair color changes, nausea (26%), anorexia (22%), vomiting (21%), fatigue (19%), weakness (14%), abdominal pain (11%), and headache (10%). 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.[109] 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.[109] In the updated analyses,[109] no differences in the frequency or severity of adverse events or grade 3/4 adverse events were seen compared with the previous report.[108]

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.[110] 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 (hazard ratio [HR], 1.047). Overall response rates (ORRs) were 31% for pazopanib and 25% for sunitinib. Pazopanib was associated with less fatigue than sunitinib (55% vs. 63%, respectively), less hand-foot syndrome (29% vs. 50%, respectively), less alteration in taste (26% vs. 36%, respectively), and less thrombocytopenia (10% vs. 34%, respectively). However, pazopanib was associated with more transaminase elevation than sunitinib (31% vs. 18%, respectively).[110] 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).[111] Median OS was 28.3 months in the pazopanib group (95% CI, 26.0–35.5) and 29.1 months in the sunitinib group (95% CI, 25.4–33.1). A subgroup analysis was performed based on risk status. In patients with favorable-risk disease, a median OS was 42.5 months for those receiving pazopanib versus 43.6 months for those receiving sunitinib. In patients with intermediate-risk disease, the median OS was 26.9 months in those who received pazopanib versus 26.1 months in those who received sunitinib. In patients with poor-risk disease, the median OS was 9.9 months in those who received pazopanib and 7.7 months in those who received sunitinib.[111]

The results of the COMPARZ trial[110,111] are supported by the results of another smaller phase III study (PISCES).[112] In the PISCES trial, 168 patients were blinded and randomized in a 1:1 manner to first-line 800 mg of pazopanib for 10 weeks followed by a 2-week break (placebo) and then 50 mg of sunitinib for 10 weeks (4 weeks on and 2 weeks off schedule) or *vice versa*.[112] 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. About 50% of the patients on pazopanib reported less fatigue compared with

about 15% of patients on sunitinib. About 45% of patients on pazopanib reported fewer changes in food taste with the drug compared with about 10% of patients on sunitinib.[112]

The NCCN Kidney Cancer Panel has listed pazopanib as a preferred category 1 option for first-line treatment of patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma.

Sunitinib as First-line Therapy for Predominantly Clear Cell Carcinoma

Sunitinib is a multikinase inhibitor targeting several receptor tyrosine kinases, including platelet-derived growth factor receptors (PDGFR-α and -β), VEGF receptors (VEGFR-1, -2, and -3), stem cell factor receptor (c-KIT), FMS-like tyrosine kinase (FLT-3), colony-stimulating factor (CSF-1R), and neurotrophic factor receptor (RET).[113,114]

Preclinical data suggested that sunitinib has anti-tumor activity that may result from both inhibition of angiogenesis and inhibition of cell proliferation.[115,116] 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 1:1 to receive either sunitinib or IFN-α.[113] The patients selected for the trial had no prior treatment with systemic therapy, good performance status, and measurable disease. The primary endpoint was PFS and secondary endpoints were patient-related outcomes, OS, response rate, and safety. The treatment arms were well balanced; patients had a median age of 60 years, and 90% had undergone prior nephrectomy. Approximately 90% of patients in the trial had either “favorable” or “intermediate” MSKCC risk features. The median PFS was 11 months for the sunitinib arm and 5 months for the IFN-α arm. The objective response rate assessed by independent review was 31% for the sunitinib arm versus 6% for the IFN-α arm. Severe adverse events (grade 3–4 toxicities) were acceptable, with neutropenia (12%), thrombocytopenia (8%), hyperamylasemia (5%), diarrhea (5%), hand-foot syndrome (5%), and hypertension (8%) being noteworthy in the sunitinib arm and fatigue being more common with IFN-α (12% vs. 7%). Updated results demonstrate a strong trend towards OS advantage of sunitinib over IFN-α in the first-line setting (26.4 months vs. 21.81 months, P = .051).[104] 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.[117]

A retrospective study using the International metastatic RCC database consortium 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).[118] In addition, no difference was observed in PFS and response rates between the two treatment options.[118]

Based on these studies and its tolerability, the NCCN Kidney Cancer Panel has also listed sunitinib as a preferred category 1 option for first-line treatment of patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma.

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

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 and forty nine patients were randomized (641 treated).[119] 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.[119]

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 objective response rate (25.5% vs. 13.1%) versus IFN-α alone. However, toxicity was greater in the combination therapy arm.[120] 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).[121]

The NCCN Kidney Cancer Panel recommends bevacizumab in combination with IFN-α as a category 1 option for first-line treatment of patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma.

Temsirolimus as First-line Therapy for Predominantly Clear Cell Carcinoma
Temsirolimus is an inhibitor of the mammalian target of rapamycin (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.[122] 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 old 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, hypercholesteremia, or hyperglycemia.

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

Sorafenib as First-line Therapy for Predominantly Clear Cell Carcinoma
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.[123-127]

A randomized phase II trial investigated the efficacy and safety of sorafenib versus IFN-α in previously untreated patients with clear cell RCC.[128] 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 primary endpoint was PFS. In the IFN-α arm, 90 patients received treatment; 56 had disease progression, 50 of whom crossed to sorafenib (400 mg twice daily). Ninety-seven patients in the sorafenib arm received treatment and had a median of 5.7 months PFS versus 5.6 months for IFN-α. The results showed that more sorafenib-treated (68.2% vs. 39.0%) patients had tumor regression.[128] Overall, the incidence of adverse events was similar between both treatment arms, although skin toxicity (rash and hand-foot skin reaction) and diarrhea occurred more frequently in patients treated with sorafenib, and flu-like syndrome occurred more frequently in the IFN-α group. Sorafenib-treated patients reported fewer symptoms and better QOL than those treated with IFN-α. Both dose escalation of sorafenib after progression and a switch to sorafenib after progression on IFN-α resulted in progression-free intervals that suggested a clinical benefit of sorafenib (as second-line therapy) after first-line treatment with IFN-α and for those who had been treated with sorafenib up front.

The NCCN Kidney Cancer Panel lists sorafenib as a category 2A option as first-line treatment for selected patients with relapsed or medically unresectable stage IV predominantly clear cell renal carcinoma.

Axitinib as First-line Therapy for Predominantly Clear Cell Carcinoma

As second-line therapy for patients with predominantly clear cell carcinoma, treatment with axitinib has clearly demonstrated greater objective response 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 3 trial was carried out in newly diagnosed patients randomized (2:1) to receive axitinib (5 mg twice daily) or sorafenib (400 mg twice daily).[129] 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).[129] 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.[129] 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.[130] 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 tolerated up to maximum 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 2A).

Subsequent Therapy for Patients with Predominantly Clear Cell Carcinoma

Cabozantinib

Cabozantinib is a small molecule inhibitor of tyrosine kinases such as VEGF-receptors, MET, and AXL. It is U.S FDA-approved for patients with progressive medullary thyroid cancer. 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).[131] 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 objective response rate was 21% for cabozantinib and 5% for everolimus (*P* < .001).[131]

The final analysis of the METEOR trial shows a statistically significant increase in OS in the cabozantinib arm.[132] Median OS of 21.4 months for those treated with cabozantinib, and 16.5 months for patients treated with everolimus (HR, 0.66; 95% CI, 0.53–0.83; *P* = .00026).[132]

An independent review has confirmed that cabozantinib treatment also resulted in improved PFS (HR, 0.51; 95% CI, 0.41–0.62; *P* < .0001) and a statistically significant increase in the objective response rate (17% vs. 3%; *P* < .001).[132]

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. 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,[131,132] the NCCN Panel has included cabozantinib as a category 1 preferred subsequent therapy option.

Nivolumab

Nivolumab is an antibody that selectively blocks the interaction between PD-1 (expressed on activated T cells) and its ligands (expressed on immune cells and tumor cells). 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.[133] 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).[133]

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.[133]

An independent analysis was carried out to determine the efficacy of nivolumab-based baseline factors such as Karnofsky performance status, Heng risk group, number of prior therapies, and specific prior therapies (ie, sunitinib, pazopanib, IL-2). A consistent OS benefit and ORR was observed across all baseline factors. [134]

The FKSI-DRS[135] 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.[133] 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. Results showed that nivolumab treatment beyond first progression was associated with reduced tumor burden in approximately 50% of patients with advanced RCC and 14% achieved greater than or equal to 30% reduction in tumor burden.[136] 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.[136] 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.[136]

Based on the results of the CheckMate 025[133] trial demonstrating superior OS with nivolumab compared with everolimus, the NCCN Panel has included nivolumab as a category 1, preferred subsequent therapy option

Lenvatinib with Everolimus as Subsequent Therapy for Predominantly Clear Cell Carcinoma

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.[137] 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).[137] The median OS was also increased for lenvatinib plus everolimus compared with everolimus monotherapy (25.5 months vs. 15.4 months; HR, 0.67: 0.42–1.08).[138] Median OS for lenvatinib alone was 18.4 months.[138]

Lenvatinib plus everolimus is listed as a category 1 recommendation for subsequent therapy by the NCCN Kidney Cancer Panel.

Axitinib as Subsequent Therapy for Predominantly Clear Cell Carcinoma

Axitinib is a selective, second-generation inhibitor of VEGFR-1, -2, and -3.[139] 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).[140] 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).[140] 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).[140] 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.

In the recently reported updated results of the same trial, median OS was 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).[141] 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).[141] The patient-reported outcomes were comparable for second-line axitinib and sorafenib.[135]

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.[142]

Axitinib is listed as a category 1 recommendation as a subsequent therapy option by the NCCN Kidney Cancer Panel.

Everolimus as Subsequent Therapy for Predominantly Clear Cell Carcinoma

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.[143] 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.[143] 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%.[143] 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.[144]

Everolimus is listed as a category 2A 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 025[133] trial demonstrated superior OS with nivolumab compared with everolimus. The METEOR trial[131] 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.

Sorafenib as Subsequent Therapy for Predominantly Clear Cell Carcinoma

Efficacy of sorafenib was studied in patients who progressed on a prior therapy (mostly cytokines) in a phase III, placebo-controlled, randomized trial, TARGET.[145,146] 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).[146] 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).[146] 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.[146] 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.[147,148] Sorafenib is listed as a category 2A subsequent therapy option.

Sunitinib as Subsequent Therapy for Predominantly Clear Cell Carcinoma
Sunitinib also has demonstrated substantial anti-tumor activity in the second-line therapy of metastatic RCC after progression on cytokine therapy.[114,149] 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.[150-154] Sunitinib is considered a category 2A subsequent therapy option.

Pazopanib as Subsequent Therapy for Predominantly Clear Cell Carcinoma
The phase III trial comparing pazopanib with placebo, detailed earlier under the section titled *Pazopanib as First-line Therapy for Predominantly Clear Cell Carcinoma*, included 202 patients who received prior cytokine therapy. The average PFS in cytokine pre-treated patients was 7.4 versus 4.2 months.[108]

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.[155] 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.[155] After a median follow-up of 16.7 months, the median PFS was 7.5 months (95% CI, 5.4–9.4 months).[155] The PFS was similar whether previous treatment was with sunitinib or bevacizumab. The estimated OS rate at 24 months was 43%.[155]

Another retrospective analysis reported data on 93 patients with metastatic RCC treated with multiple lines of prior targeted therapies.[156] 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 subsequent therapy option.

Other Agents as Subsequent Therapy for Predominantly Clear Cell Carcinoma
Phase II trials have shown benefit of bevacizumab monotherapy after prior treatment with a cytokine.[157] Bevacizumab is a category 2B subsequent therapy option. A phase II trial suggested benefit to temsirolimus therapy after prior treatment with a cytokine.[158] A phase III trial (INTORSECT) compared the efficacy of temsirolimus to sorafenib following first-line sunitinib as a treatment for patients with RCC.[159] 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).[159] 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.[160] The NCCN Panel considers temsirolimus a category 2B subsequent therapy option.

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.[161] 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.[161]

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.[162] 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 was 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).[162] 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).[162] These results support the currently recommended treatment of first-line sunitinib followed by everolimus at progression.

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

Systemic Therapy for Patients with Non-Clear Cell Carcinoma

Clinical trials of targeted agents have predominantly focused on patients with clear cell histology versus non-clear cell due to the high prevalence of the clear cell RCC. 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.

Systemic Therapy for Non-Clear Cell Carcinoma

There are now two randomized phase II studies showing activity of systemic therapy in patients with non-clear cell RCC. In addition, systematic reviews, meta-analysis of phase II studies, and retrospective studies with targeted agents 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 carcinoma.

Sunitinib

Data from expanded-access trials, phase II trials, and retrospective analyses support clinical activity of sunitinib.[163-170]

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).[168] 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.[164]

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.[171] Overall, median PFS, the primary endpoint of the trial, was longer in patients treated with sunitinib (8.3 vs. 5.6 months).[171] 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. Whereas patients with poor-risk features did better with everolimus treatment compared with sunitinib (median, 6.1 vs. 4.0 months).[171] In the ESPN trial, patients with metastatic non-clear cell RCC were randomized to treatment with everolimus or sunitinib.[172] 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).[172] In patients having tumors with *no* sarcomatoid features (n = 49), the median OS was 31.6 months with sunitinib and 10.5 months with everolimus (P = .075).

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

Temsirolimus

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.[122,173] 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.[174]

Temsirolimus is a category 1 recommendation for non-clear cell carcinoma 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.

Everolimus

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.[175-177]

The efficacy and safety of everolimus in patients with metastatic RCC of non-clear cell histology was evaluated in a subgroup of patients (n = 75) enrolled in the RAD1001 Expanded Access Clinical Trial in RCC (REACT).[175] 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.[175] 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%).[175] 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.[177] The histology of the enrolled patients included papillary (n = 29), chromophobe (n = 8), collecting duct (n = 2), sarcomatoid (n = 4), and unclassified (n = 6).[177] The median PFS was 5.2 months. The objective response rate was 10.2% with all of the responses being partial. Twenty five patients (51%) had stable disease; 16 patients (32.7%) progressed despite everolimus.[177] Adverse events reported in the trial, greater than Grade 3, included anemia (10.2%), hyperglycemia (8.2%), infection (6.1%), and pneumonitis (4.1 %).[177] Interim results from an ongoing phase II trial (RAPTOR) suggest that everolimus (10 mg once daily) provides an anti-tumor effect in previously untreated patients with advanced papillary RCC. The median PFS as assessed by the investigators was 7.3 months (95% CI, 5.6–15.2). Safety and PFS of patients still on treatment as assessed by independent reviewers is ongoing. The NCCN Panel has included everolimus as an option for patients with non-clear cell RCC (category 2A).

Sorafenib

Phase II trials and retrospective analyses support clinical activity of sorafenib[178-180] 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.[164]

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

Pazopanib and Axitinib

The clinical benefit of pazopanib or axitinib has not yet been established in patients with non-clear carcinoma. There are ongoing clinical trials evaluating the efficacy of pazopanib and axitinib in patients with non-clear cell carcinoma in first-line and second-line settings.[181-183] A retrospective analysis of an Italian multicenter cohort of non-clear cell RCC patients found treatment with Pazopanib to be effective and safe.[184]

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

Erlotinib

The efficacy of erlotinib, an oral epidermal growth factor receptor (EGFR) TKI, was studied in patients with advanced papillary RCC.[185] 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.[185] 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 an option for first-line therapy for patients with relapsed or medically unresectable stage IV non-clear cell carcinoma (category 2A).

Other Therapies for Non-Clear Cell Carcinoma

A small phase II trial studied bevacizumab monotherapy in patients with papillary RCC. This study closed early due to 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.[186]

The NCCN Panel has included bevacizumab as a therapeutic option for patients with non-clear cell RCC (category 2A).

The NCCN Panel recently added nivolumab, cabozantinib, and lenvatinib plus everolimus as treatment options (category 2A) for patients with non-clear cell carcinoma.

Chemotherapy for Metastatic Renal Cell Carcinoma

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.[187] Sarcomatoid RCC is associated with a poor prognosis.[188-191] 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.[192-197] The potential role of sunitinib in combination gemcitabine has been investigated in a phase II trial of RCC with sarcomatoid features.[198] The results show that the combination was well tolerated and is active especially in patients with rapidly progressing disease.[198] There are ongoing trials studying sunitinib in combination with gemcitabine compared to sunitinib alone in patients with sarcomatoid features.[199]

Among the non-clear cell histologies, renal medullary carcinoma is extremely rare, comprising approximately 2% of all primary renal tumors in young people.[200,201] Metastatic disease is seen at presentation in 95% of patients.[200,201] 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.[202-205] 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.[206] The results showed a response rate of 26% and an OS of 10.5 months.[206]

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 partial responses to cytotoxic chemotherapy have been observed (gemcitabine in combination with carboplatin or cisplatin; or paclitaxel with carboplatin) in patients with other non-clear cell subtypes such as collecting duct or medullary subtypes.

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 evaluation 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 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 solitary brain metastasis 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.[207]

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.[208-210] 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.[211,212]

The role of bone-modifying agents such as bisphosphonates (eg, zoledronic acid) has been well established in this setting.[213,214] 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 1,776 patients with bone metastases from a wide range of cancer types, including patients with RCC (6%) not previously treated with a bisphosphonate.[215] 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).[215]

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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