NCCN National Comprehensive Cancer Network®

The NCCN

Kidney Cancer

Clinical Practice Guidelines in Oncology™

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Overview

In 2008, an estimated 54,390 Americans were diagnosed with kidney cancer and 13,010 died of the disease in the United States.[1] Renal cell carcinoma (RCC) comprises approximately 2% of all malignancies, with a median age at diagnosis of 65 years. The rate of RCC has increased 2% per year for the past 65 years. The reason for this increase is unknown. Approximately 90% of renal tumors are RCC, and 85% of these are clear cell tumors.[2] Other, less-common cell types include papillary, chromophobe, and Bellini (collecting) duct tumors. Collecting duct carcinoma comprises fewer than 1% of all cases. Medullary renal carcinoma is a variant of collecting duct renal carcinoma and was initially described as occurring in patients who are sickle cell–trait positive.

Smoking and obesity are among the risk fac-

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Key Words

NCCN Clinical Practice Guidelines, renal cell carcinoma, clear cell tumors, kidney disease, nephrectomy

(*JNCCN* 2009;7:618–630)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

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

Please Note

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Disclosures for the NCCN Kidney Cancer Guidelines Panel

At the beginning of each NCCN guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and on-line. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Kidney Cancer Guidelines Panel members can be found on page 630. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at www.nccn.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.nccn.org.

tors for RCC development. Several hereditary types of RCC also exist, with von Hippel-Lindau disease (VHL) the most common, caused by a mutation in the *VHL* gene predisposing to clear cell carcinoma.[3,4]

The overall 5-year relative survival rate for the period between 1996 and 2003 from 17 SEER geographic areas was 65.5%.[5] The most important prognostic determinants of 5-year survival are tumor grade, local extent of the tumor, presence of regional nodal metastases, and evidence of metastatic disease at presentation. RCC primarily metastasizes to the lung, bone, brain, liver, and adrenal gland.[3]

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. Common complaints that lead to the detection of a renal mass are 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 may indicate VHL disease, and these patients should be referred to a hereditary cancer clinic for further evaluation.

Renal tumors may also be identified on an imaging study (e.g., CT or ultrasound) performed to evaluate other conditions (see page 620). As the use of imaging methods has become more widespread, the frequency of incidental detection of RCC has increased. These

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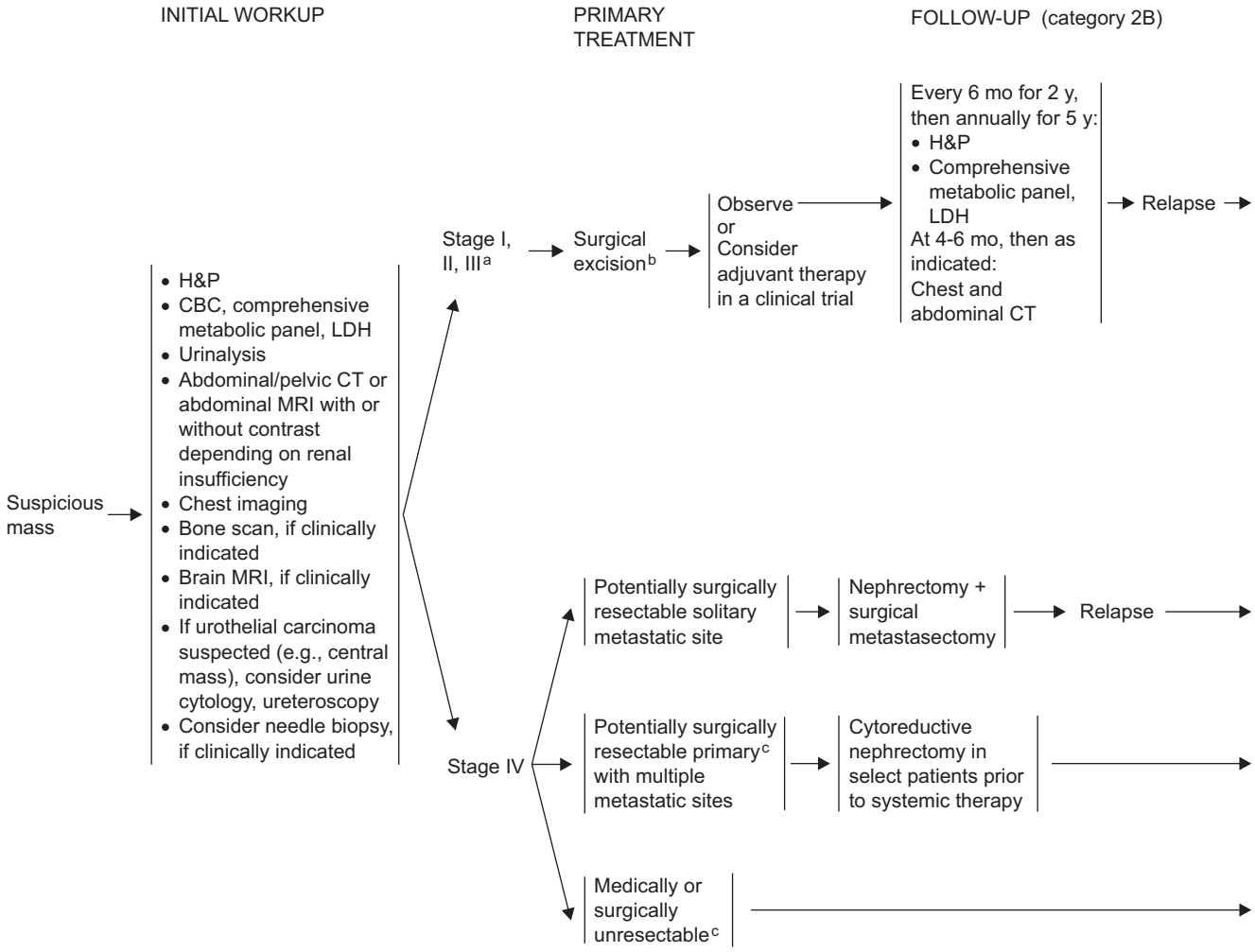
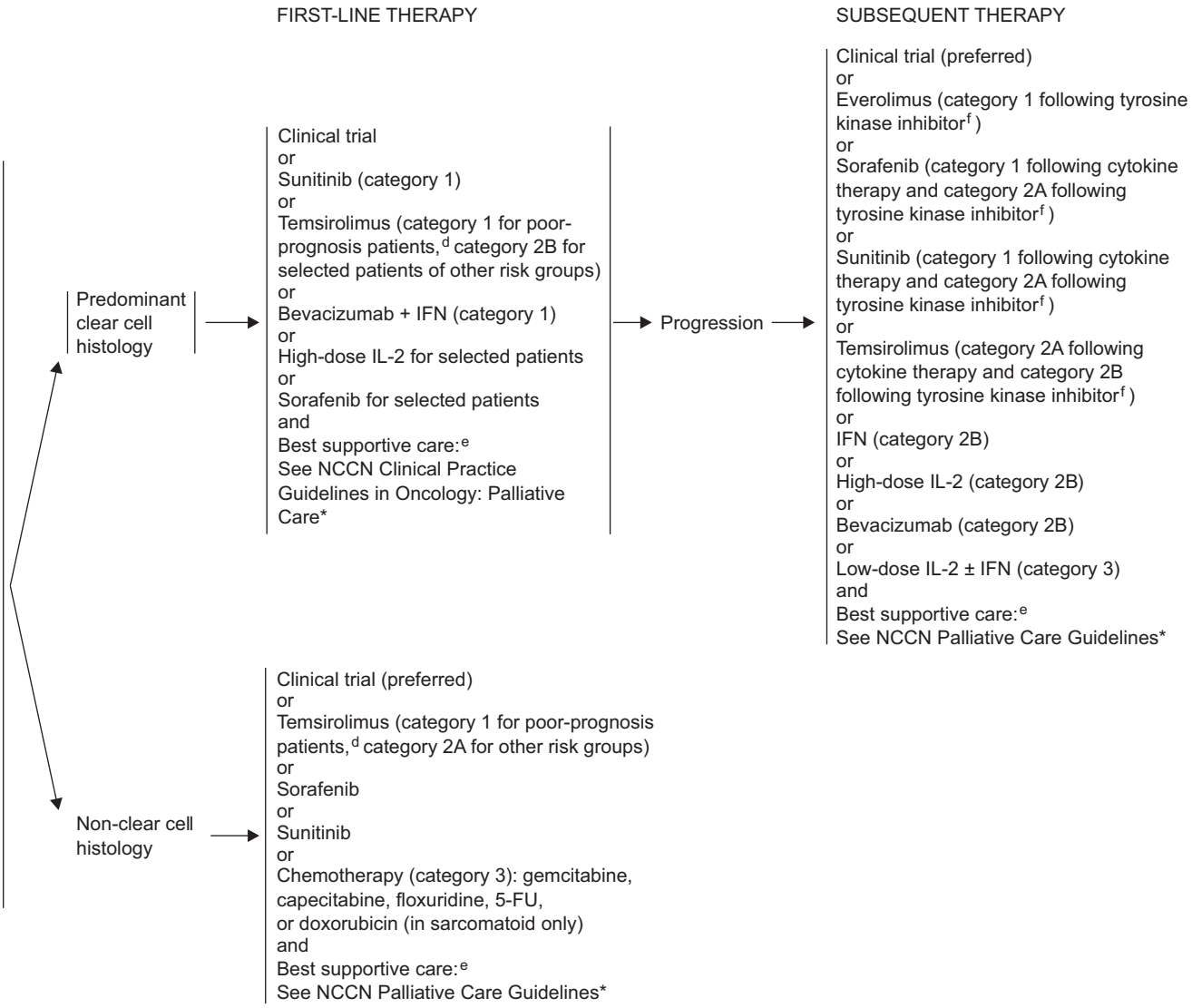


[a]Patients are encouraged to participate in clinical trials.
[b]See Principles of Surgery (page 622).
[c]Individualized treatment based upon symptoms and extent of metastatic disease.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.



*For the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org.

[d] Poor-prognosis patients, defined as those with ≥ 3 predictors of short survival. See Predictors of Short Survival (page 622).
[e] Best supportive care can include palliative RT, metastasectomy, or bisphosphonates for bony metastases.
[f] For example, sorafenib or sunitinib.

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PRINCIPLES OF SURGERY

- Nephron-sparing surgery may be indicated in selected patients, for example:
  - Multiple primaries
  - Uninephric state
  - Renal insufficiency
  - Selected patients with small unilateral tumors
- Lymph node dissection is optional.
- Adrenal gland may be left if uninvolved and tumor is not high-risk, based on size and location.
- Special teams may be required for extensive inferior vena cava involvement.
- Observation or emerging energy-ablative techniques (e.g., cryosurgery or radiofrequency ablation) can be considered for patients who are not surgical candidates.
- Emerging energy-ablative techniques (e.g., cryosurgery, radiofrequency ablation) are currently considered an option by some experts for selected small tumors, although a rigorous comparison with surgical resection (i.e., total or partial nephrectomy using open or laparoscopic techniques) has not been performed.

PREDICTORS OF SHORT SURVIVAL[1]

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/L)
- Interval of less than a year from original diagnosis to the start of systemic therapy
- Karnofsky performance score ≤ 70
- ≥ 2 sites of organ metastasis

[1] 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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small low-stage carcinomas may be treated with more conservative surgical approaches, such as nephron-sparing techniques, discussed in later sections.

A thorough physical examination should be performed with special attention to detecting supraclavicular adenopathy, abdominal mass, lower extremity edema, a varicocele, or subcutaneous nodules. Laboratory evaluation includes a CBC count, comprehensive metabolic panel (including serum calcium, liver function studies, lactate dehydrogenase [LDH], and serum creatinine), coagulation profile, and urinalysis.

CT of the abdomen and pelvis with and without contrast and chest imaging (either chest radiograph or CT scan) are essential studies in the initial workup. Abdominal MRI is used to evaluate the inferior vena cava if tumor involvement is suspected, or it can be used instead of CT to detect renal masses and for staging (see staging table, available online, in these guidelines, at www.nccn.org [ST-1]) when contrast material cannot be administered because of allergy or renal insufficiency.[6,7] A central renal mass may suggest the presence of a urothelial cell carcinoma; if so, urine cytology or uteroscopy should be considered.

A bone scan is not routinely performed unless patients have an elevated serum alkaline phosphatase or complains of bone pain. CT or MRI of the brain is performed if the history or physical examination suggests brain metastases. A PET scan is not a routine part of the initial workup.

Fine-needle biopsy[8] has been shown to have a limited role in the workup of patients with RCC, but may be considered in selected cases.

Primary Treatment and Staging

CT-guided needle biopsy of the kidney or other accessible sites or cytoreductive nephrectomy can be used to diagnose patients with suspected RCC (see page 620). Selected patients with metastases can be diagnosed during cytoreductive nephrectomy.

Surgical resection remains the only effective therapy for clinically localized RCC; with options including radical nephrectomy and nephron-sparing surgery (see page 622). A radical nephrectomy includes a perifascial resection of the kidney, perirenal fat, regional lymph nodes, and ipsilateral adrenal gland. Although lymph node dissection is not considered therapeutic, it provides prognostic information, because virtually all patients with nodal involvement subsequently relapse with distant metastases despite lymphadenectomy. Also, ipsilateral adrenal gland resection may only be necessary for patients who have large upper-pole tumors or abnormal-appearing adrenal glands shown on CT. Radical nephrectomy is the preferred treatment if the tumor extends into the inferior vena cava. Approximately one half of patients with these tumors experience long-term survival. Resection of a caval or atrial thrombus often requires the assistance of cardiovascular surgeons and may entail the techniques of veno–venous or cardiopulmonary bypass, with or without circulatory arrest. Patients considered for resection of a caval or atrial tumor thrombus should undergo surgery performed by experienced teams because treatment-related mortality approaches 10%, depending on the local extent of the primary tumor and the level of vena caval extension.

Originally, nephron-sparing surgery was indicated only in clinical settings in which a radical nephrectomy would render patients functionally anephric, necessitating dialysis (see page 622). These settings include RCC in a solitary kidney, RCC in one kidney with inadequate contralateral renal function, and bilateral synchronous RCC. However, nephron-sparing surgery has been used increasingly in patients with T1a and T1b renal tumors (i.e., < 7 cm in greatest dimension) and a normal contralateral kidney, with equivalent outcomes to radical nephrectomy.[9–11] Nephron-sparing surgery is most appropriate for tumors located over the upper or lower pole or in a peripheral location. Patients with a hereditary form of RCC, such as VHL disease, also should be considered for nephron-sparing therapy.

Patients in satisfactory medical condition should undergo surgical excision of stage I through III tumors. However, a small set of elderly or infirm patients with small tumors may be offered surveillance alone or energy-ablative, minimally invasive techniques, such as radiofrequency ablation[12,13] or cryoablation[14] (see page 622).

The estimated average 5-year survival rates for patients with RCC are 96% for stage I disease, 82% for stage II, 64% for stage III, and 23% for stage IV.[3]

Management after Surgical Excision of Stages I Through III Tumors

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.[15] The median time to relapse after surgery is 1 to 2 years, with most relapses occurring within 3 years. Longer disease-free intervals between diagnosis and recognition of metastatic disease are associated with longer projected survival.

Adjuvant treatment after nephrectomy has no established role in patients who have undergone a complete resection of their tumor. No systemic therapy has been shown to reduce the likelihood of relapse. Randomized trials comparing adjuvant interferon (IFN)-α or high-dose interleukin (IL)-2 with observation alone in patients who had locally advanced, completely resected RCC showed that no delay in time to relapse or improvement in survival was associated with adjuvant therapy.[16–18] Observation remains standard care after nephrectomy, and eligible patients should be enrolled in randomized clinical trials, if available. Radiation therapy after nephrectomy is not beneficial, even in patients with nodal involvement or who have undergone incomplete tumor resection.

Follow-up for patients with completely resected disease includes an abdominal and chest CT scan obtained approximately 4 to 6 months after surgery to serve as a baseline, then as clinically indicated. Patients are seen periodically, and each visit should include a history, physical examination, and comprehensive metabolic panel (e.g., blood urea nitrogen, serum creatinine, calcium levels, LDH, liver function tests; see page 620).

Management of Stage IV Disease

Patients with stage IV disease are also candidates for surgery. For example, lymph nodes suspected for disease on CT may be hyperplastic and not involved with the tumor; therefore, patients with minimal regional adenopathy can be surgical candidates. 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 initially present with primary RCC and a solitary site of metastasis or develop a solitary recurrence after nephrectomy. Sites of solitary metastases that are amenable to this approach include the lung, bone, and brain. Both 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 metastatic site experience recurrence at the primary or metastatic site. However, long-term survival has been seen in some patients.[19] In some instances, radiation therapy may be administered after bone metastases.[20]

Cytoreductive nephrectomy before systemic therapy is recommended in patients with a potentially surgically resectable primary and multiple metastases (see page 620). Randomized trials showed a benefit for cytoreductive nephrectomy followed by IFN therapy. The SWOG (8949) and EORTC trials randomized patients with metastatic disease to undergo either nephrectomy followed by IFN therapy or treatment with IFN therapy alone. A combined analysis of these trials showed that median survival favored the surgery plus IFN group (13.6 vs. 7.8 months for IFN alone).[21–23]

Patient selection is important to identify patients who might benefit from cytoreductive therapy. Patients most likely to benefit from nephrectomy before systemic therapy are those with lung-only metastases, good prognostic features, and good performance status. The role of cytoreductive nephrectomy and patient selection may warrant assessment in the setting of targeted therapy.

Patients with hematuria or other symptoms related to the primary tumor may be considered for palliative nephrectomy. Treatment for the palliation of symptoms, especially in patients with marginal performance status and evidence of metastatic disease, includes optimal pain management (see NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain; for the most current version of these guidelines, please visit the NCCN Web site at www.nccn.org).

First-Line Therapy

Until recently, systemic treatment options for metastatic RCC were limited to cytokine therapy and clinical trials of novel agents. Randomized trials studied various combinations and dosages of IL-2 and IFN in patients with metastatic, recurrent, or unresectable clear cell RCC (see page 621). These studies suggested that high-dose IL-2 produces higher response rates, including complete remission in some patients,[25] compared with low-dose IL-2.[24–26] This is the only drug reported in literature to produce durable remissions. Therefore, patients with a high Karnofsky performance status (> 80), especially those with low-volume or lung-predominant disease, may be offered high-dose IL-2. Enrolling patients in clinical trials and administering high-dose IL-2 therapy for selected

patients are category 2A recommendations.

Although cytokines have been standard care for approximately 15 years, targeted therapy with tyrosine kinase inhibitors have recently been used in first- and second-line treatments. Three of these agents have been approved by the FDA for treating advanced RCC: sunitinib malate, sorafenib tosylate, and temsirolimus. A fourth, bevacizumab, recently showed benefit in a pivotal phase III trial. Risk stratification of patients is important in therapy selection. The most widely used model for risk stratification is the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria.[27] The risk factors or predictors of short survival (see page 622) include high blood LDH level (> 1.5 times the upper limit of normal), high blood calcium level (corrected Ca^{++} > 10 mg/dL or 2.5 mmol/L), anemia, duration of less than a year from diagnosis to the need for systemic treatment, and low Karnofsky performance status (< 80%). Patients with none of these risk factors are placed in the favorable- or good-risk group, 1 to 2 risk factors in the intermediate group, and 3 or more risk factors in the poor-risk group.

Treatment for Clear Cell Carcinoma: Sunitinib malate is a multikinase inhibitor. It selectively inhibits several receptor tyrosine kinases, platelet-derived growth factor receptors (PDGFR-α, PDGFR-β), vascular endothelial growth factor receptors (VEGFR-1, -2, -3), stem cell factor receptor (c-KIT), FMS-like tyrosine kinase (Flt3), colony stimulating factor-1R, and the neurotrophic factor receptor. Preclinical data suggested that sunitinib malate has antitumor activity that may result from inhibition of both angiogenesis and cell proliferation.[28,29] A large, multinational phase III trial was conducted to further evaluate the efficacy of sunitinib in previously untreated patients with metastatic RCC.[30] A total of 750 patients with metastatic (all risk) clear cell–histology RCC were randomized to receive either sunitinib or IFN-α.

Patients selected for the trial had no prior treatment with systemic therapy, a good performance status, and measurable disease. The primary end point was progression-free survival (PFS), and secondary end points were patient-related outcomes, overall survival, response rate, and safety. Stratification factors were LDH levels, ECOG performance status of 0 or 1, and nephrectomy status. Patients were randomized to receive oral sunitinib (n = 375) or IFN-α (n = 375). The treatment arms were well balanced; patients had a median age of 60 years, and 90% had undergone prior nephrectomy. Approximately 90% of patients on 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 through 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 more common with IFN-α (12% vs. 7%).

Updated results of this study presented at the 2008 ASCO annual meeting show an overall survival advantage of sunitinib in the first-line setting.[31] The overall survival of patients treated with sunitinib was longer (26.4 vs. 21.81 months).[31] Based on these studies and its tolerability, sunitinib has been given a category 1 recommendation for first-line treatment of patients with relapsed or medically unresectable stage IV renal cancer with predominant clear cell; for non–clear cell histology it is a category 2A recommendation.

Sorafenib tosylate is small molecule that inhibits multiple isoforms of the intracellular serine/threonine kinase Raf (including C-Raf and B-Raf) and other receptor tyrosine kinases, including VEGFR-1, -2, and -3, PDGFR-β, Flt3, and c-KIT.[32–36]

A randomized phase II trial investigated the efficacy and safety of sorafenib versus IFN in previously untreated patients with clear cell RCC.[37] Patients (n = 189) were randomized to continuous oral sorafenib (400 mg, twice daily) or IFN, with an option of dose escalation of sorafenib to 600 mg, twice daily or crossover from IFN to sorafenib (400 mg, twice daily) on disease progression. The primary end point was PFS. In the IFN arm, 90 of 92 patients underwent treatment; 56 had disease progression, of which 50 crossed to sorafenib (400 mg, twice daily). All 97 patients in the sorafenib arm underwent treatment; median PFS was 5.7 versus 5.6 months for sorafenib (400 mg, twice daily) versus IFN, respectively.

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 group. Median PFS was 5.3 months in patients (n = 50) who crossed over from IFN to sorafenib (400 mg, twice daily). The median PFS for patients (n = 44) with dose escalation to 600 mg twice daily was 3.6 months. The 600 mg twice daily dose was well tolerated. Further analyses of possible benefits from sorafenib dose escalation are required in a larger number of patients. Sorafenib is recommended (category 2A) for selected patients as first-line treatment with relapsed or medically unresectable stage IV renal cancer with both predominant clear cell and non–clear cell RCC.

Temsirolimus is a potent and specific inhibitor of the mammalian target of rapamycin (mTOR) protein and was approved for treatment of RCC by the FDA on May 30, 2007. mTOR regulates nutritional needs, cell growth, and angiogenesis through down- or up-regulating various proteins, including hypoxia-inducible factor (HIF)-1.[38] The panel added temsirolimus as an option in first-line therapy for patients with relapsed or medically unresectable stage IV renal cancer with both predominant clear cell and non–clear cell histology. Efficacy and safety of temsirolimus was shown at a second interim analysis of the global Advanced Renal Cell Carcinoma (ARCC) trial, a phase III, multicenter, randomized, open-label study in previously untreated patients with advanced RCC who had 3 or more of the following 6 prognostic factors:[39] duration of less than 1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, correct calcium of greater than 10 mg/dL, LDH greater than 1.5 times the upper limit of normal, and more than 1 metastatic organ site.

This trial randomized 626 patients to 1 of the following 3 arms: IFN-α alone (n = 207); temsirolimus, 25 mg, alone (n = 209); or combination temsirolimus, 15 mg, and IFN (n = 210). Patients were stratified for prior nephrectomy and geographic region; 70% were younger than 65 years and 69% were men. Temsirolimus was infused intravenously over 30 to 60 minutes weekly until disease progression or unacceptable toxicity. Premedication with an antihistamine was recommended. The group of patients who received temsirolimus alone showed a significant improvement in overall survival, which was the primary end point of the study. Median overall survival was 10.9 months for patients treated with temsirolimus alone versus 7.3 months for those treated with IFN alone. Combination temsirolimus and IFN did not result in a significant increase in overall survival compared with IFN alone. PFS was a secondary end point, and median PFS increased from 3.1 months on the IFN-alone arm to 5.5 months on temsirolimus-alone arm. The combination did not result in a significant increase in overall survival compared with IFN-α alone and was associated with an increase in multiple adverse reactions. The most common grade 3 or 4 adverse events, seen more in patients treated with temsirolimus than those treated with IFN-α, included rash, stomatitis, pain, infection, peripheral edema, thrombocytopenia and neutropenia, hyperlipidemia, hypercholesteremia, and hyperglycemia. Based on these data, panel members included temsirolimus as a category 1 recommendation as first-line treatment for poor prognosis patients with metastatic clear cell and non–clear cell RCC.

Bevacizumab is an anti–VEGF-A recombinant monoclonal antibody that binds and neutralizes circulating VEGF-A. In a phase II randomized trial, 116 patients with metastatic RCC refractory to IL-2 therapy were randomized to receive low-dose bevacizumab (n = 37), high-dose bevacizumab (n = 39), or placebo (n = 40).[40] The group treated with high-dose bevacizumab showed a significant prolongation of the time to disease progression compared with the placebo group. No significant difference in the time to progression of disease was seen in the group treated with low-dose antibody compared with the group treated with placebo.

For patients given high-dose bevacizumab, low-dose bevacizumab, and placebo, the probabilities of being progression-free were 64%, 39%, and 20%, respectively, at 4 months, and 30%, 14%, and 5%, respectively, at 8 months. Bevacizumab yielded a 10% response rate (with several patients having prolonged periods of stability or minor responses), and a PFS of 4.8 compared with 2.5 months with placebo. High-dose bevacizumab prolonged tumor progression by a factor of 2.55 compared with placebo. No significant differences in overall survival were seen between the groups. Adverse effects of all grades, including hypertension (36%), asymptomatic proteinuria (64%), hematuria (13%), and epistaxis (20%), were also significantly higher in the high-dose bevacizumab group.

Subsequently, a randomized, double-blinded, multicenter, phase III trial (AVOREN) compared bevacizumab plus IFN-α with placebo plus IFN-α in

649 patients (641 treated).[41] 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%). A trend toward improved overall survival was also observed. No new side effects were observed with the combination, compared with those anticipated with each agent.

In the United States, a similarly conducted trial was performed by CALGB.[42] This trial randomized previously untreated patients to receive either IFN-α or the combination of bevacizumab plus IFN. Bevacizumab plus IFN produced a superior PFS (8.5 vs. 5.2 months) and higher objective response rate (25.5% vs. 13.1%) than IFN monotherapy. Toxicity, however, was greater in the combination therapy arm. The final survival analysis for this study is awaited.

Bevacizumab in combination with IFN-α is recommended as a category 1 recommendation as first-line therapy for patients with relapsed or medically unresectable stage IV disease with predominant clear cell histology.

Treatment for Non–Clear Cell Carcinoma: Enrollment in clinical trials is the preferred strategy for non–clear cell RCC. Temsirolimus is the only agent that has shown activity in patients with this histology. Subset analysis of the global ARCC trial[39] showed benefit of temsirolimus in not only clear cell but also non–clear cell RCC. Activity occurred irrespective of age and, again, most benefit in patients with poor-risk features. Sunitinib and sorafenib are category 2A recommendations in this setting. Chemotherapy as first-line therapy is a category 3 recommendation for patients with relapsed or medically unresectable stage IV disease with non–clear cell histology. Results of clinical trials evaluating capecitabine[43,44] or gemcitabine with or without 5-FU[45] for metastatic RCC or a doxorubicin-based regimen[46] for sarcomatoid RCC suggest minor or modest activity in patients experiencing progression after treatment with immunotherapy.

Second-Line Therapy

Clinical trials are preferred for second-line and subsequent therapy for metastatic disease.

Everolimus (RAD001) is an orally administered inhibitor of mTOR. It received FDA approval on March 30, 2009, for patients with advanced RCC for whom treatment with sorafenib or sunitinib failed. The international, multicenter, double-blinded, randomized phase III RECORD 1 trial compared everolimus with placebo for treating metastatic RCC in patients whose disease had progressed during treatment with sunitinib or sorafenib.[47] Patients (n = 410) were randomly assigned in a 2:1 ratio to everolimus (10 mg, once daily) or placebo, and the primary end point was PFS. The median PFS assessed by an independent review committee favored everolimus (4.0 months; 95% CI, 3.7–5.5, vs. 1.9 months; 95% CI, 1.8–1.9).[47] The most common adverse events reported in patients taking everolimus (mostly of mild or moderate severity) were stomatitis (40% vs. 8% in the placebo group), rash (25% vs. 4%), and fatigue (20% vs. 16%).[47] Based on these trial data, everolimus is a category 1 recommendation after tyrosine kinase therapy.

A randomized phase II discontinuation trial evaluated effects of sorafenib treatment versus placebo on 202 patients with metastatic RCC.[48] After 12 weeks, patients with changes in bidimensional tumor measurements less than 25% were randomized to sorafenib or placebo for an additional 12 weeks. Patients with 25% tumor shrinkage continued on sorafenib, whereas those with progressive disease discontinued the drug. The remaining potential responders were randomized to either continue or stop treatment with sorafenib. Therefore, only 65 patients were ultimately randomized. At 24 weeks, 50% of the sorafenib group was progression-free compared with 18% of the placebo group, representing a clinically and statistically significant difference.

These results led to the placebo-controlled, randomized, phase III TARGET trial (Treatment Approaches in RCC Global Evaluation Trial).[49] The 905 selected patients had measurable disease, clear cell histology, experienced 1 prior systemic therapy failure in the past 8 months and had an ECOG performance status of 0 to 1, and a good or intermediate prognosis. Almost all patients had undergone nephrectomy.

The primary end point of the trial was to assess overall survival, with PFS as the secondary end point. In a preliminary report, tumor control (stable disease or partial response) with sorafenib was achieved in 80% of patients, although only 2% experienced a partial response.[50] Sorafenib significantly prolonged median PFS compared with placebo (24 vs. 12 weeks), and median survival improvement was preliminarily reported (19.3 vs. 15.9 months). Benefit was evident across all subsets evaluated.

Crossover from placebo to sorafenib was permitted owing to the magnitude of effect on PFS. The patients

who crossed over showed a 30% improvement in survival. In the placebo arm assessed at crossover, the median survival was 19.3 months for sorafenib versus 14.3 months for placebo. Adverse effects were grade 3 to 4 hand–foot syndrome (5%), fatigue (2%), and hypertension observed (1%), respectively. Although the final results of the trial clearly show the PFS benefit of sorafenib in patients with advanced RCC, the overall survival benefit was confounded by the crossover.[51] However, a planned secondary analysis adjusted for crossover by censoring the placebo-control patients showed the overall survival benefit of sorafenib.[51]

The aforementioned phase II and III trials evaluating the effectiveness of sorafenib were conducted primarily in patients after progression on prior cytokine therapy. Sunitinib also showed substantial antitumor activity in second-line metastatic RCC.[52] Sorafenib and sunitinib are considered category 1 when used after cytokine therapy, and category 2A when used after a prior tyrosine kinase inhibitor therapy.

Temsirolimus is category 2A recommendation after cytokine therapy and category 2B after tyrosine kinase inhibitor. IFN-α, high-dose IL-2, and bevacizumab are also considered category 2B recommendations, and low-dose IL-2 with or without IFN-α is category 3 (see page 621).

The mainstay of therapy for all patients with metastatic RCC is supportive care, including surgery for patients with solitary brain metastasis, spinal cord compression, or impending or actual fractures in weight-bearing bones. Also, radiation therapy along with bisphosphonates is considered for palliation, particularly of painful bone metastases. The frequency of clinic visits or radiographic and laboratory assessments depends on patient individual needs.

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Individual Disclosures for the NCCN Kidney Cancer Panel

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The NCCN guidelines staff have no conflicts to disclose.