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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Kidney Cancer

Version 2.2011

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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.

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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The 2.2011 version of the Kidney Cancer Guidelines represents the addition of the updated discussion section - [MS-1](#).

Updates in Version 1.2011 of the NCCN Kidney Cancer Guidelines from Version 1.2010 include:

General

- UCLA Integrated Staging System (UISS) surveillance protocol was removed from the guidelines.

[KID-1:](#)

- For stage I-III, the primary treatment was separated into Stage IA and IB and Stage II, III and the corresponding treatment options were added.
- Footnote c, “See Principles of Surgery (KID-A)” was added to the page.
- Footnote d, “Can be open or robotic/laparoscopic” was added to the page.
- Footnote e was modified by adding, “Alternate follow-up schemes have been proposed”.

[KID-3:](#)

- For predominant clear cell histology:
 - ▶ First-line therapy, footnote i, “Patients with excellent performance status and normal organ function” was added.
 - ▶ Subsequent therapy, the category for bevacizumab was changed from a category 2B to category 2A following cytokine therapy and category 2B following tyrosine kinase inhibitor.

[KID-4:](#)

- For non-clear cell histology, systemic therapy:
 - ▶ “Erlotinib” was added with a category 3 designation.
 - ▶ Chemotherapy for sarcomatoid only (category 3) was revised to include combination therapy with gemcitabine + doxorubicin and single-agent capecitabine, floxuridine, fluorouracil, and doxorubicin were removed.

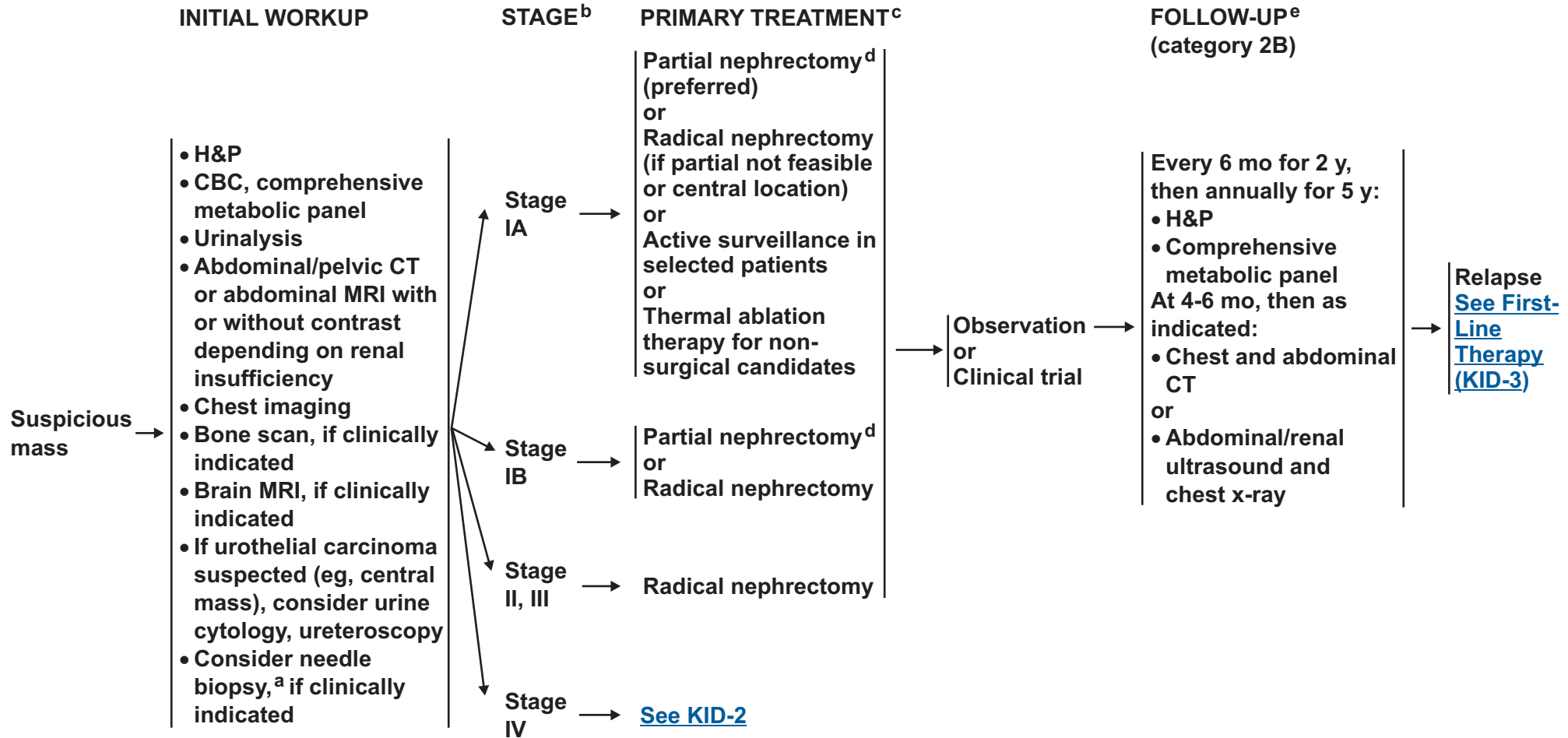
[KID-A:](#)

• Principles of surgery:

- ▶ First bullet was modified by adding, “Small unilateral tumors (*T1a and selected patients T1b*)” and “*uninephric state, renal insufficiency, bilateral renal masses, familial renal cell cancer*”.
- ▶ Second bullet, “Nephron-sparing surgery should be performed by a surgeon proficient in the procedure” is new to the page.
- ▶ Third bullet was modified by adding, “but is recommended for patients with adenopathy on preoperative imaging or palpable/visible-adenopathy at time of surgery.
- ▶ Sixth bullet was modified by adding, “Thermal ablative techniques are associated with higher local recurrence rate than conventional surgery” with two corresponding references.
- ▶ Last bullet, “Generally, patients who would be candidates for cytoreductive nephrectomy prior to systemic therapy have: excellent performance status (ECOG PS < 2), no brain metastasis” is new to the guidelines.

[ST-1:](#)

- The staging has been updated to the 2010 American Joint Committee on Cancer (AJCC) TNM Staging System for Kidney Cancer.



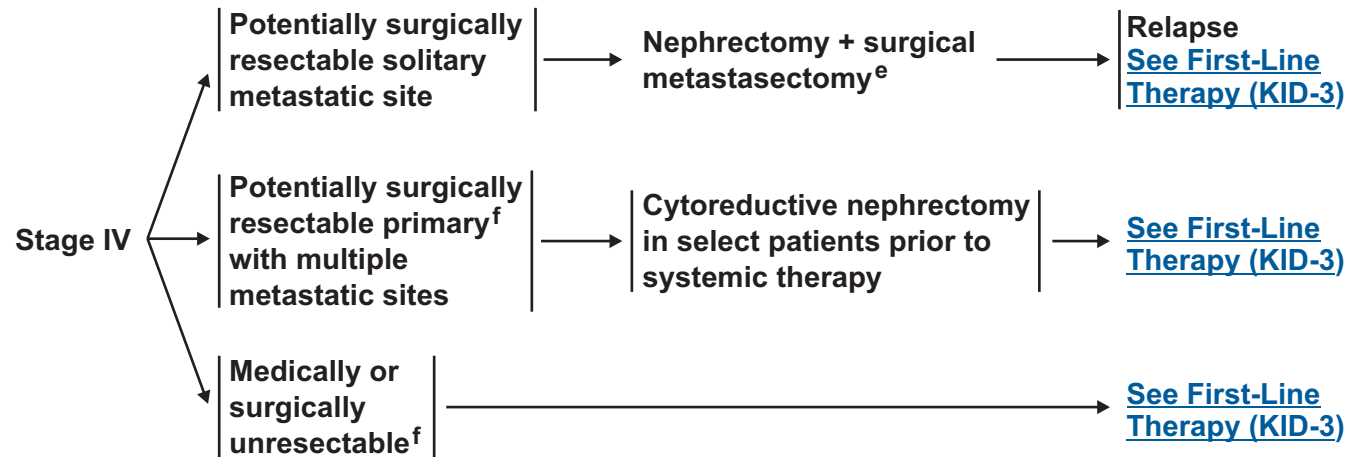
^aBiopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance, cryosurgery, and radiofrequency ablation strategies.
^bPatients are encouraged to participate in clinical trials.
^c[See Principles of Surgery \(KID-A\)](#).
^dCan be open or robotic/laparoscopic.
^eNo single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient and tumor characteristics. Alternate follow-up schemes have been proposed.

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



STAGE^b

PRIMARY TREATMENT^c



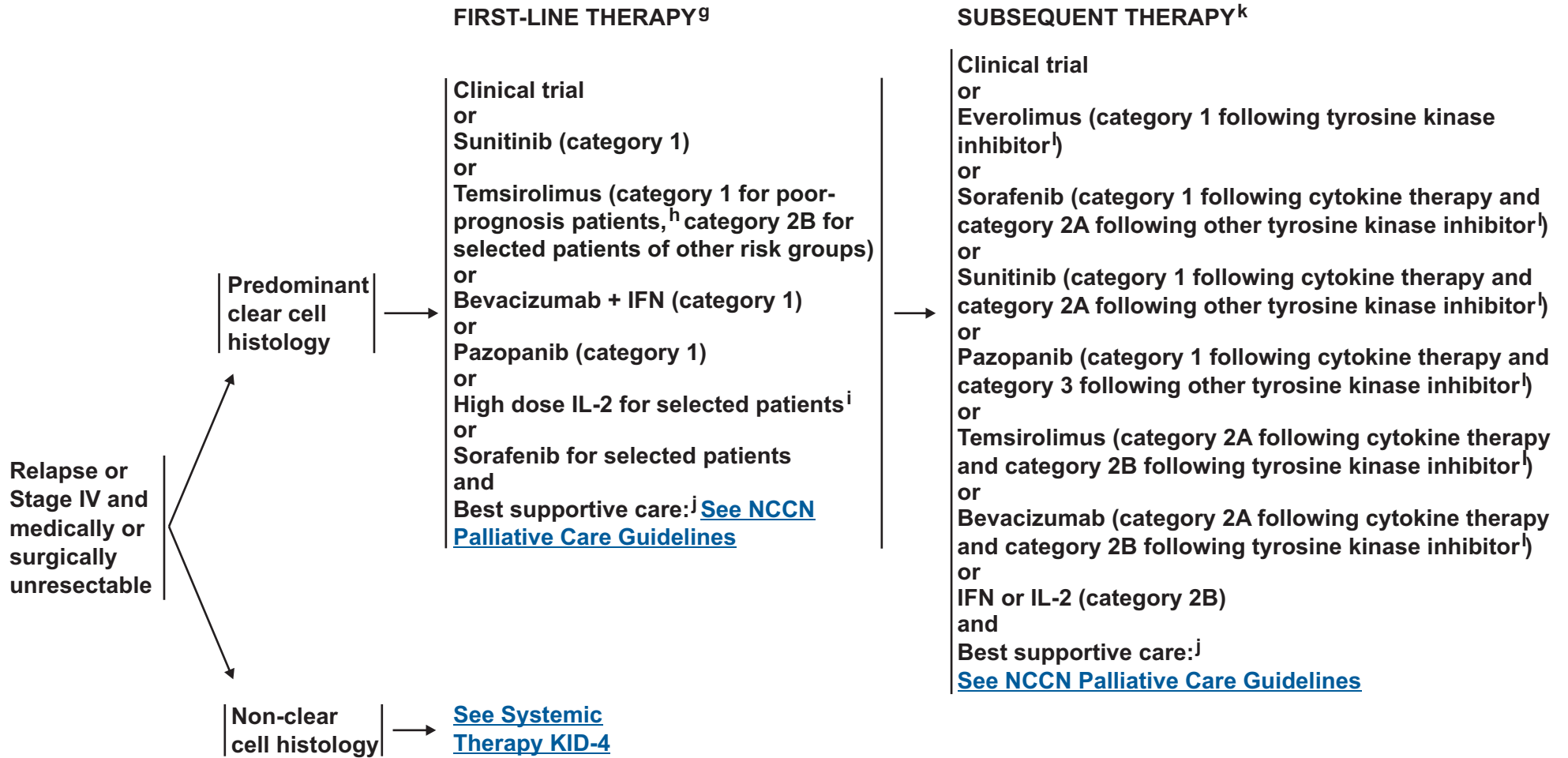
^bPatients are encouraged to participate in clinical trials.

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

^eNo single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient and tumor characteristics. Alternate follow-up schemes have been proposed.

^fIndividualized treatment based upon symptoms and extent of metastatic disease.

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



⁹Category 1 recommendations are listed in order of FDA approval.

^hPoor-prognosis patients, defined as those with ≥ 3 predictors of short survival. [See Predictors of Short Survival \(KID-B\)](#).

ⁱPatients with excellent performance status and normal organ function.

^jBest supportive care can include palliative RT, metastasectomy, or bisphosphonates for bony metastases.

^kTyrosine kinase inhibitors with a category 1 designation are listed in order of FDA approval.

^lCurrently available tyrosine kinase inhibitors include: sorafenib, sunitinib, or pazopanib.

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

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



SYSTEMIC THERAPY

Relapse or
Stage IV and
medically or
surgically
unresectable



Non-clear
cell histology



Clinical trial (preferred)
or
Temsirolimus (category 1 for poor-prognosis patients,^m
category 2A for other risk groups)
or
Sorafenib
or
Sunitinib
or
Pazopanib (category 3)
or
Erlotinib (category 3)
or
Chemotherapy in sarcomatoid only (category 3):
gemcitabine + doxorubicin
and
Best supportive care:^j [See NCCN Palliative Care Guidelines](#)

^jBest supportive care can include palliative RT, metastasectomy, or bisphosphonates for bony metastases.

^mPoor-prognosis patients, defined as those with ≥ 3 predictors of short survival. [See Predictors of Short Survival \(KID-B\)](#).

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

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



PRINCIPLES OF SURGERY

- **Nephron-sparing surgery is appropriate in selected patients, for example:**
 - ▶ **Small unilateral tumors (T1a and selected patients T1b)**
 - ▶ **Uninephric state, renal insufficiency, bilateral renal masses, familial renal cell cancer**
- **Nephron-sparing surgery should be performed by a surgeon proficient in the procedure.**
- **Regional lymph node dissection is optional but is recommended for patients with adenopathy on preoperative imaging or palpable/visible adenopathy at time of surgery.**
- **Adrenal gland resection may be omitted if adrenal is uninvolved and tumor is not high risk on the basis of size and location.**
- **Special teams may be required for extensive inferior vena cava involvement.**
- **Observation or ablative techniques (eg, cryosurgery or radiofrequency ablation):**
 - ▶ **Can be considered for patients with clinical stage T1 renal lesions who are not surgical candidates.**
 - ▶ **Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance, cryosurgery, and radiofrequency ablation strategies.**
 - ▶ **Rigorous comparison with surgical resection (ie, total or partial nephrectomy by open or laparoscopic techniques) has not been done.**
 - ▶ **Thermal ablative techniques are associated with a higher local recurrence rate than conventional surgery.^{1,2}**
- **Generally, patients who would be candidates for cytoreductive nephrectomy prior to systemic therapy have:**
 - ▶ **Excellent performance status (ECOG PS < 2)**
 - ▶ **No brain metastasis**

¹Campbell 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.

²Kunkle 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.

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



PREDICTORS OF SHORT SURVIVAL¹

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

¹Hudes G, Carducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007; 356(22):2271-2281.

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

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

**Table 1****American Joint Committee on Cancer (AJCC)
TNM Staging System for Kidney Cancer (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 a single 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 T3	N1 N0 or N1	M0 M0
Stage IV	T4 Any T	Any N Any N	M0 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 and 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.

Discussion

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.

Overview

An estimated 58,240 Americans will be diagnosed with renal cancer and 13,040 will die of the disease in the United States in 2010.¹ Renal cell carcinoma (RCC) comprises approximately 2-3% of all malignancies, with a median age at diagnosis of 65 years. The rate of RCC has increased by 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 duct (collecting duct) tumors. Collecting duct carcinoma comprises less than 1% of kidney cancer cases. 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 among the risk factors for RCC development. Several hereditary types of RCC also exist, with von Hippel-Lindau disease (VHL) the most common, caused by an autosomal dominant constitutional mutation in the *VHL* gene that predisposes to clear cell carcinoma and other proliferative vascular lesions.^{3,4}

The overall 5-year relative survival rate of patients with renal and pelvic cancers for the period between 1999-2005 from 17 SEER geographic areas was 69.4%.⁵ The most important prognostic determinants of 5-year survival are the 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.⁴

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 computed tomographic (CT) scan. As the use of imaging methods (e.g., abdominal/pelvic CT or ultrasound) has become more widespread, the frequency of incidental detection of RCC has increased. 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.

A thorough physical examination should be performed along with obtaining a complete medical history of the patient. Laboratory evaluation includes a complete blood cell 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 magnetic resonance imaging (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 renal insufficiency.^{6,7} A central renal mass may suggest the presence of urothelial carcinoma; if so, urine cytology or uteroscopy should be considered. A bone scan is not routinely performed unless the patient has 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. Needle-biopsy may be considered to confirm diagnosis of RCC and guide active surveillance strategies.

The estimated average 5-year survival rates in renal cell carcinoma is 96% for patients presenting with stage I, 82% for stage II, 64% for stage III, and 23% for stage IV disease.⁴

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.

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. Approximately one half of patients with these tumors experience long-term survival.

The lymph node dissection is not considered therapeutic but does provide prognostic information, because virtually all patients with nodal involvement subsequently relapse with distant metastases despite lymphadenectomy. The updated European Organization for the Research and Treatment of Cancer (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, time to progression of disease, or progression-free survival between the two study groups.⁸ However, primary tumor pathological features such as nuclear grade, sarcomatoid component, tumor size, stage and presence of tumor necrosis are all factors that influence the likelihood of regional lymph node involvement at the time of radical nephrectomy.⁹

The NCCN Kidney Cancer panel recommends lymph node dissection for patients with palpable or CT-detected enlarged lymph nodes as well as to obtain adequate staging information in those with normal-appearing nodes.

Ipsilateral adrenal gland resection should be considered for patients with large upper-pole tumors or abnormal-appearing adrenal glands appearing on CT.¹⁰⁻¹² Adrenalectomy is not indicated when imaging shows a normal adrenal gland or if the tumor is not high-risk, based on size and location.

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. However, nephron-sparing surgery has been used increasingly in patients with T1a and T1b renal tumors (i.e., up to 7 cm in greatest dimension) and a normal contralateral kidney, with equivalent outcomes to radical nephrectomy.¹³⁻¹⁶ Radical nephrectomy should not be employed when nephron sparing can be achieved.

Patients with a hereditary form of RCC, such as VHL syndrome, should also be considered for nephron-sparing therapy. Partial nephrectomy has well established oncologic outcomes data comparable to radical nephrectomy,^{14, 17-19} which can lead to an increased risk of chronic kidney disease^{20, 21} that is associated with increased risks of cardiovascular morbidity and mortality, according to population-based studies. When compared with radical nephrectomy, partial nephrectomy can achieve preserved renal function, decreased overall mortality and reduced frequency of cardiovascular events.^{22, 23}

The goals of nephron sparing surgery should be optimal locoregional tumor control while minimizing ischemia time to ideally less than 30 minutes.²⁴ 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. Active surveillance (with delayed intervention if indicated) or thermal ablation techniques such as cryo- or radiofrequency ablation are alternative strategies for selected patients, particularly the elderly and those with competing health risks.

The NCCN Kidney Cancer Panel has addressed the utility of each treatment modality in the context of tumor stages: Stage IA, Stage IB, and Stages II & III.

Management of Stage IA Disease

The NCCN panel members prefer surgical excision by partial nephrectomy for the management of clinical stage IA 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 uninephric 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 IA RCC if a partial nephrectomy is not feasible technically as determined by the urologic surgeon.

Other options in selected patients with Stage IA RCC include active surveillance and thermal ablation. 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.²⁵

Although distant recurrence-free survival rates are comparable, thermal ablation has been associated with an increased risk of local recurrence compared to results with conventional surgery.^{26, 27} Judicious patient selection and counseling remain of paramount importance for these less invasive technologies.



Management of Stage IB Disease

Surgery by either radical nephrectomy or partial nephrectomy (whenever feasible) is the standard of care for clinical T1b tumors.

Management of Stage II and III Disease

Radical nephrectomy is the preferred treatment if the tumor extends into the inferior vena cava and is the standard of care for patients with stage II and III renal tumors. 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 may reach 10%, depending on the local extent of the primary tumor and the level of vena caval extension.

Management after Surgical Excision of Stages I–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. The median time to relapse after surgery is 1 to 2 years, with most relapses occurring within 3 years.

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) or high-dose interleukin (IL-2) 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.²⁸⁻³⁰ Observation remains standard care after nephrectomy, and eligible

patients should be offered enrolled in randomized clinical trials. There are a number of ongoing and recently-completed clinical trials exploring 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.

Follow-up for patients with completely resected disease includes an abdominal and chest CT scan obtained approximately 4 to 6 months after surgery and then as clinically indicated. Chest x-ray and ultrasound may also be performed to assess patients especially in patients with small tumors and low risk of recurrence.

No single follow-up plan is appropriate for all patients; therefore, individual follow-up plans should be developed that take into account the size of the primary tumor, the extent of extent of extrarenal spread, tumor histology, and relative risk of relapse. Patients are seen every 6 months for the first 2 years after surgery and annually thereafter and each visit should include a history, physical examination, and comprehensive metabolic panel (e.g., blood urea nitrogen, serum creatinine, calcium levels, LDH, and liver function tests).

Alternate surveillance programs have been proposed, such as the surveillance protocol based on the UCLA Integrated Scoring System (UISS).³¹ The UISS is an evidence-based system in which patients are stratified based on the 1997 TNM stage, grade, and Eastern Cooperative Oncology Group (ECOG) performance status into low, intermediate, or high risk groups for developing recurrence or metastases post-surgical treatment of localized or locally advanced RCC.³¹ The use of this protocol allows selective use of imaging and appropriately targeting those patients most in need of intensive surveillance.



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 and 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 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 at the primary or metastatic site, but long-term progression-free survival has been reported in a subset of patients following radiotherapy for solitary bone metastases.³²

Primary Treatment of Advanced or Stage IV Disease

Cytoreductive nephrectomy before systemic therapy is recommended generally in patients with a potentially surgically resectable primary and multiple resectable metastases. Randomized trials showed a benefit of cytoreductive nephrectomy in patients who received IFN- α therapy after surgery. In similar Phase III trials, the Southwest Oncology Group (SWOG) and the EORTC randomized patients with metastatic disease to undergo either nephrectomy followed by IFN- α therapy or treatment with IFN- α alone.³³⁻³⁵ 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).³³⁻³⁶

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.³⁷ 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 as well as from a variety of publications by other groups suggests that nephrectomy also provides benefit to patients who undergo other forms of immunotherapy.³⁸ 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. 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.

First-line Therapy for Patients with Predominantly Clear Cell Carcinoma

Cytokine Therapy

Until recently, 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 a number of murine tumor models³⁹ and subsequently in patients with RCC.⁴⁰⁻⁴² With both IFN- α and IL-2, objective response rates of 5-27% have been reported.⁴²⁻⁴⁴ Although these agents have been helpful for some patients, in most cases the clinical benefit is modest 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 aggressive IFN- α or infusional IL-2, with superior responses at the cost of much 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.^{39, 43, 45} 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 co-morbidities, tumor histology (predominantly clear cell), Memorial Sloan Kettering Cancer Center (MSKCC)⁴⁶ or University of California Los Angeles (UCLA) Survival After Nephrectomy and Immunotherapy (SANI) risk scores,^{38, 47} and the patient's attitude toward risk.

According to the NCCN Kidney Cancer panel, for 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 are used widely in first and second-line treatments. To date, six such agents have been approved by the FDA for the treatment of advanced RCC: sunitinib, sorafenib, pazopanib, temsirolimus, everolimus, and bevacizumab in combination with interferon.

Tumor histology and risk stratification of patients is important in targeted therapy selection. The most widely used model for risk

stratification is the MSKCC model.⁴⁶ The MSKCC model classifies patients according the presence or absence of 5 adverse prognostic factors - Karnofsky performance status 70 or less, serum lactate dehydrogenase level (LDH) greater than 1.5 times the upper limit of normal (ULN), hemoglobin level below normal, corrected serum calcium level above the ULN, and time from diagnosis and nephrectomy to therapy lesser than 1 year. Patients with none of these factors are considered low risk or 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, based on shorter survival compared to the good and intermediate risk patients.

Sunitinib as first-line therapy for predominantly clear cell carcinoma

Sunitinib is a multi-kinase inhibitor targeting a number of receptor tyrosine kinases including platelet-derived growth factor receptors (PDGFR- α and - β), vascular endothelial growth factor 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).^{48, 49}

Preclinical data suggested that sunitinib has anti-tumor activity that may result from both inhibition of angiogenesis and inhibition of cell proliferation.^{50, 51} 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 .⁴⁸ The patients selected for the trial had no prior treatment with systemic therapy, good performance status and measurable disease. The primary endpoint was progression-free survival (PFS), and secondary endpoints were patient-related outcomes, overall survival (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 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 by independent review was 31% for the sunitinib arm vs. 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 demonstrate an overall survival advantage of sunitinib over IFN- α in the first-line setting (26.4 months vs. 21.81 months).⁴⁴ Recent data from an expanded access trial that was performed before the drug became commercially available 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.⁵²

Based on these studies and its tolerability, the NCCN Kidney Cancer panel has listed sunitinib as a category 1 option for first line treatment of patients 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. The U.S. FDA approved bevacizumab in combination with IFN- α for treatment of advanced renal cell cancer on August 3, 2009. 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).⁵³ 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 versus 21.3 months for IFN- α), although the difference did not reach statistical significance.⁵³

In the United States, a similar trial was performed by the Cancer and Leukemia Group B, 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.⁵⁴ The survival data for this trial were recently updated, showing 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).⁵⁵

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

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. Pazopanib received FDA approval on October 19, 2009 for treatment of patients with advanced renal cell carcinoma. The safety and effectiveness of pazopanib was evaluated in a phase III trial open-label, international, multi-center 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. Progression-free survival was prolonged significantly with pazopanib in the overall study population, averaging 9.2 months versus 4.2 months for patients assigned to placebo.⁵⁶ The treatment-naïve subpopulation of 233 patients, randomized 2:1 to pazopanib versus placebo had a median PFS 11.1 months on pazopanib vs. 2.8 months on placebo.⁵⁶ The objective response rate was 30% with pazopanib and 3% with placebo (all results 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%). A 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. Pazopanib also has been associated with heart rhythm irregularities.

The NCCN Kidney Cancer panel members include pazopanib 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 and was approved for treatment of renal cell carcinoma by the U.S. FDA on May 30, 2007. mTOR regulates micronutrients, cell growth, apoptosis and angiogenesis by its downstream effects on a variety of proteins. Efficacy and safety of temsirolimus was demonstrated 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 6 unfavorable prognostic factors.⁵⁷ 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 lower limit of normal, corrected calcium of greater than 10 mg/dL, LDH > 1.5 times the ULN, metastasis to one or more than one organ site. Six hundred and twenty six patients were randomized equally to receive IFN- α alone, or 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 less 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 overall survival 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 this data, the NCCN Kidney Cancer panel members have included temsirolimus as a category 1 recommendation for first-line treatment of poor prognosis 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.⁵⁸⁻⁶²

A randomized phase II trial investigated the efficacy and safety of sorafenib versus IFN- α in previously untreated patients with clear cell RCC.⁶³ One hundred and eighty nine patients were randomized to continuous oral sorafenib (400 mg bid) or IFN- α , with an option of dose escalation of sorafenib to 600 mg bid or crossover from IFN- α to sorafenib (400 mg bid) 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 bid). Ninety-seven patients in the sorafenib arm received treatment and had median 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.⁶³ Progression-free rates for sorafenib versus IFN- α were 90.0% vs. 70.4%, 45.9% vs. 46.5%, and 11.5% vs. 30.4% at 3, 6, and 12 months, respectively.⁶³ 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 quality of life 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 for sorafenib (as second-line therapy) in patients who failed IFN- α treatment as well as those who had been treated with sorafenib up-front.

According to the NCCN Kidney Cancer panel members, for selected patients with relapsed or medically unresectable stage IV predominantly clear cell renal carcinoma, sorafenib is listed as a first line treatment option with a category 2A designation.

Subsequent Therapy for Patients with Predominantly Clear Cell Carcinoma*Everolimus as subsequent therapy*

Everolimus (RAD001) is an orally administered inhibitor of mTOR. It received FDA approval on March 30, 2009, for patients with advanced RCC after failure of treatment with sorafenib or sunitinib. In the RECORD 1 trial, an international, multicenter, double-blind, randomized phase III trial, everolimus was compared with placebo for the treatment of metastatic renal cell carcinoma in patients whose disease had progressed on treatment with sunitinib or sorafenib.⁶⁴ Four hundred ten were randomly assigned 2:1 to receive either everolimus or placebo, and the primary end point was progression-free survival. The median PFS assessed by an independent review committee was in favor of everolimus, 4.0 vs. 1.9 months.⁶⁴ The most common adverse events reported in patients on everolimus (mostly of mild or moderate severity) were stomatitis in 40% vs. 8% in the placebo group, rash 25% vs. 4%, and fatigue 20% vs. 16%.⁶⁴

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.⁶⁵ Serious adverse events (in \geq 5% of patients) with everolimus, independent of causality, included infections (all types, 10%), dyspnea (7%), and fatigue (5%).



Based on these data, everolimus is a category 1 recommendation following tyrosine kinase therapy according to the NCCN Kidney Cancer panel members.

Tyrosine kinase inhibitors as subsequent therapy

Efficacy of sorafenib was studied in patients who progressed on a prior therapy (mostly cytokines) in a phase III placebo-controlled randomized trial, TARGET (Treatment Approaches in RCC Global Evaluation Trial).⁶⁶ Nine hundred and three patients were enrolled in this trial. The patients selected had measurable disease, clear cell histology, failed one prior systemic therapy in the last 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 endpoint of the trial was to assess overall survival, and the secondary endpoint was PFS. Sorafenib significantly prolonged median PFS compared with placebo (5.9 months vs. 2.8 months) as well as median OS in the preliminary analysis (19.3 vs. 15.9 months) for all patient subsets; with the large difference in PFS, crossover to the sorafenib treatment arm was permitted, which likely resulted in the failure of this trial to demonstrate an overall survival benefit for sorafenib in the final analysis. With censoring of crossover data, the median OS was 19.3 months for sorafenib versus 14.3 months for placebo.⁶⁷ Adverse effects were grade 3 to 4 hand-foot syndrome, fatigue, and hypertension observed in 5%, 2%, and 1% of patients, respectively.⁶⁸ This study showed the effectiveness of sorafenib in a clinical setting comprising primarily of patients who progressed on prior cytokine therapy.

Sunitinib also has demonstrated substantial anti-tumor activity in the second-line therapy of metastatic RCC following progression after cytokine therapy.^{49, 69} Studies investigating the sequential use of

sunitinib and sorafenib mostly are retrospective. There are prospective data, although limited, 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 as well as slightly different toxicity spectra that sometimes permit tolerance of one agent over another.⁷⁰⁻⁷⁶ Sorafenib and sunitinib are considered category 1 by the NCCN Kidney Cancer panel when used after cytokine therapy and category 2A when used after a prior tyrosine kinase inhibitor therapy.

The phase III trial comparing pazopanib with placebo, detailed earlier under the section titled “*Pazopanib as first-line therapy for predominantly clear cell carcinoma*” (page MS-7 and MS-8), included 202 patients who received prior cytokine therapy. The average PFS in cytokine pre-treated patients was 7.4 vs. 4.2 months.⁵⁶ Based on the results from this trial, the NCCN Kidney Cancer panel members consider pazopanib as a category 1 option following cytokine therapy. However following tyrosine kinase failure, the use of pazopanib is listed as category 3, since there no data are available in this setting.

Other agents as subsequent therapy

Temsirolimus is a category 2A recommendation following cytokine therapy and category 2B following tyrosine kinase inhibitor. Bevacizumab is a category 2A recommendation following cytokine therapy and category 2B following tyrosine kinase inhibitor. IFN- α , IL-2, are category 2B recommendations.

Systemic Therapy for Patients with Non-Clear Cell Carcinoma

Enrollment in clinical trials is the preferred strategy for non-clear cell RCC.

*Temsirolimus for predominantly non-clear cell carcinoma*

Temsirolimus is the only agent that has shown activity in patients with non-clear cell RCC. Subset analysis of the global ARCC trial demonstrated benefit of temsirolimus not only in clear cell renal carcinoma but also in non-clear cell.^{57,77} There was activity irrespective of age and most benefit was seen in patients with poor risk features. Based on this data, the NCCN Kidney Cancer panel members have included temsirolimus as first-line treatment for patients with metastatic non-clear cell. It is a category 1 recommendation for non-clear cell carcinoma patients with poor prognosis features (according to MSKCC risk criteria) and category 2A for patients belonging to other prognostic risk groups.

Tyrosine kinase inhibitors for predominantly non-clear cell carcinoma

Sunitinib and sorafenib are category 2A recommendations for treatment naïve patients with non clear cell carcinoma. Recent data from an expanded access trial revealed that sunitinib is safe and efficacious in subgroups of patients with treated brain metastases, non-clear cell histology, and poor performance status.⁵²

The efficacy of pazopanib has not yet been studied in patients with non-clear carcinoma. Therefore based on extrapolation, the NCCN Kidney Cancer panel has included pazopanib with a category 3 designation as a first line therapy for patients with relapsed or medically unresectable stage IV disease with non-clear cell histology.

The efficacy of erlotinib, an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, was studied in patients with advanced papillary RCC.⁷⁸ Fifty two patients were treated with erlotinib given

orally once daily. The overall response rate was 11% (five of 45 patients; 95% CI, 3% to 24%), and the disease control rate (defined as stable disease for 6 weeks, or confirmed partial response or complete response using RECIST [Response Evaluation Criteria in Solid Tumors]) was 64%. The median OS was 27 months.⁷⁸ 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 now included erlotinib as an option for first-line therapy for patients with relapsed or medically unresectable stage IV with non-clear cell histology with a category 3 designation.

Chemotherapy for predominantly non-clear cell carcinoma

Gemcitabine in combination with doxorubicin has shown moderate activity in patients with sarcomatoid tumors.⁷⁹⁻⁸¹ The NCCN Kidney Cancer panel has listed chemotherapy with gemcitabine and doxorubicin as an option for first line therapy for patients with relapsed or medically unresectable stage IV disease with non-clear cell histology with a category 3 designation.

Supportive Care

Supportive care remains a mainstay of therapy for all patients with metastatic RCC. 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. 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. Also, radiation therapy along with bisphosphonates^{82,83} is considered for palliation, particularly of



painful bone metastases. The frequency of clinic visits or radiographic and laboratory assessments depends on the individual needs of the patient.

Treatment for the palliation of symptoms, especially in patients with marginal performance status and evidence of metastatic disease, includes optimal pain management (See [NCCN Adult Cancer Pain Guidelines](#)).

References

- Jemal A, Siegel R, Xu J and Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277-300. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20610543>
- Karumanchi SA, Merchan J and Sukhatme VP. Renal cancer: molecular mechanisms and newer therapeutic options. *Curr Opin Nephrol Hypertens* 2002;11:37-42. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11753085>
- Choyke PL, Glenn GM, Walther MM, et al. Hereditary renal cancers. *Radiology* 2003;226:33-46. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12511666>
- DeVita VT Jr HS, Rosenberg SA. *Cancer Principles and Practice of Oncology*. (ed 8th). Philadelphia, PA: Lippincott Williams & Wilkins; 2008. Available at: <http://www.cancerppo8.com>
- Horner MJ RL, Krapcho M, Neyman N, Aminou R, Howlader N, Altekruse SF, Feuer EJ, Huang L, Mariotto A, Miller BA, Lewis DR, Eisner MP, Stinchcomb DG, Edwards BK SEER Cancer Statistics Review, 1975-2006, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2006/ based on November 2008 SEER data submission, posted to the SEER web site, 2009.
- Hricak H, Demas BE, Williams RD, et al. Magnetic resonance imaging in the diagnosis and staging of renal and perirenal neoplasms. *Radiology* 1985;154:709-715.
- Janus CL and Mendelson DS. Comparison of MRI and CT for study of renal and perirenal masses. *Crit Rev Diagn Imaging* 1991;32:69-118. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1863349>
- Blom JH, van Poppel H, Marechal JM, et al. Radical nephrectomy with and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. *Eur Urol* 2009;55:28-34. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18848382>
- Blute ML, Leibovich BC, Cheville JC, et al. A protocol for performing extended lymph node dissection using primary tumor pathological features for patients treated with radical nephrectomy for clear cell renal cell carcinoma. *J Urol* 2004;172:465-469. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15247704>
- Kuczyk M, Munch T, Machtens S, et al. The need for routine adrenalectomy during surgical treatment for renal cell cancer: the Hannover experience. *BJU Int* 2002;89:517-522. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11942955>
- Kuczyk M, Wegener G and Jonas U. The therapeutic value of adrenalectomy in case of solitary metastatic spread originating from primary renal cell cancer. *Eur Urol* 2005;48:252-257. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15936136>
- O'Malley RL, Godoy G, Kanofsky JA and Taneja SS. The necessity of adrenalectomy at the time of radical nephrectomy: a systematic review. *J Urol* 2009;181:2009-2017. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19286216>
- Hollingsworth JM, Miller DC, Dunn RL, et al. Surgical management of low-stage renal cell carcinoma: Technology does not supersede biology. *Urology* 2006;67:1175-1180. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16765177>
- Leibovich BC, Blute ML, Cheville JC, et al. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. *J Urol* 2004;171:1066-1070. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14767272>
- Shuch B, Lam JS and Belldegrun AS. Open partial nephrectomy for the treatment of renal cell carcinoma. *Curr Urol Rep* 2006;7:31-38. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16480666>
- Chen DY and Uzzo RG. Optimal management of localized renal cell carcinoma: surgery, ablation, or active surveillance. *J Natl Compr Canc*



Netw 2009;7:635-642; quiz 643. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/19555585>

17. Dash A, Vickers AJ, Schachter LR, et al. Comparison of outcomes in elective partial vs radical nephrectomy for clear cell renal cell carcinoma of 4-7 cm. BJU Int 2006;97:939-945. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/16643474>

18. Lau WK, Blute ML, Weaver AL, et al. Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. Mayo Clin Proc 2000;75:1236-1242. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/11126830>

19. Lee CT, Katz J, Shi W, et al. Surgical management of renal tumors 4 cm. or less in a contemporary cohort. J Urol 2000;163:730-736. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/10687966>

20. Huang WC, Levey AS, Serio AM, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. Lancet Oncol 2006;7:735-740. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/16945768>

21. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-1305. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/15385656>

22. Weight CJ, Lieser G, Larson BT, et al. Partial nephrectomy is associated with improved overall survival compared to radical nephrectomy in patients with unanticipated benign renal tumours. Eur Urol 2010;58:293-298. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/20546991>

23. Weight CJ, Larson BT, Gao T, et al. Elective partial nephrectomy in patients with clinical T1b renal tumors is associated with improved overall survival. Urology 2010;76:631-637. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/20451967>

24. Funahashi Y, Hattori R, Yamamoto T, et al. Ischemic renal damage after nephron-sparing surgery in patients with normal contralateral kidney. Eur Urol 2009;55:209-215. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/18706758>

25. Rais-Bahrami S, Guzzo TJ, Jarrett TW, et al. Incidentally discovered renal masses: oncological and perioperative outcomes in patients with delayed surgical intervention. BJU Int 2009;103:1355-1358. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/19239459>

26. Campbell SC, Novick AC, Belldegrun A, et al. Guideline for management of the clinical T1 renal mass. J Urol 2009;182:1271-1279. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/19683266>

27. Kunkle DA and Uzzo RG. Cryoablation or radiofrequency ablation of the small renal mass : a meta-analysis. Cancer 2008;113:2671-2680. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/18816624>

28. Clark JI, Atkins MB, Urba WJ, et al. Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. J Clin Oncol 2003;21:3133-3140. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/12810695>

29. Messing EM, Manola J, Wilding G, et al. Phase III study of interferon alfa-NL as adjuvant treatment for resectable renal cell carcinoma: an Eastern Cooperative Oncology Group/Intergroup trial. J Clin Oncol 2003;21:1214-1222. Available at
<http://www.ncbi.nlm.nih.gov/pubmed/12663707>

30. Trump D, Elson, P, Propert, K, Pontes, J, Crawford, E, Wilding, G, Loehrer, P Randomized, controlled trial of adjuvant therapy with lymphoblastoid interferon (L IFN) in resected, high risk renal cell carcinoma (HR-RCC) [abstract]. ASCO Annual Meeting; 1996:Abstract 648. Available at:
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_de tail_view&confID=29&abstractID=9072

31. Lam JS, Shvarts O, Leppert JT, et al. Postoperative surveillance protocol for patients with localized and locally advanced renal cell carcinoma based on a validated prognostic nomogram and risk group stratification system. *J Urol* 2005;174:466-472; discussion 472; quiz 801. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16006866>
32. Fossa SD, Kjolseth I and Lund G. Radiotherapy of metastases from renal cancer. *Eur Urol* 1982;8:340-342. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6183119>
33. Flanigan RC, Mickisch G, Sylvester R, et al. Cyto-reductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol* 2004;171:1071-1076. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14767273>
34. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001;345:1655-1659. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11759643>
35. Mickisch GH, Garin A, van Poppel H, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* 2001;358:966-970. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11583750>
36. Polcari AJ, Gorbonos A, Milner JE and Flanigan RC. The role of cyto-reductive nephrectomy in the era of molecular targeted therapy. *Int J Urol* 2009;16:227-233. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19207114>
37. Culp SH, Tannir NM, Abel EJ, et al. Can we better select patients with metastatic renal cell carcinoma for cyto-reductive nephrectomy? *Cancer* 2010;116:3378-3388. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20564061>
38. Leibovich BC, Han KR, Bui MH, et al. Scoring algorithm to predict survival after nephrectomy and immunotherapy in patients with metastatic renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer* 2003;98:2566-2575. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14669275>
39. Rosenberg SA, Mule JJ, Spiess PJ, et al. Regression of established pulmonary metastases and subcutaneous tumor mediated by the systemic administration of high-dose recombinant interleukin 2. *J Exp Med* 1985;161:1169-1188. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3886826>
40. Dutcher JP, Fisher RI, Weiss G, et al. Outpatient subcutaneous interleukin-2 and interferon-alpha for metastatic renal cell cancer: five-year follow-up of the Cytokine Working Group Study. *Cancer J Sci Am* 1997;3:157-162. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9161781>
41. Negrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. *Groupe Francais d'Immunotherapie. N Engl J Med* 1998;338:1272-1278. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9562581>
42. Fyfe G, Fisher RI, Rosenberg SA, et al. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol* 1995;13:688-696. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7884429>
43. McDermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2005;23:133-141. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15625368>
44. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:3584-3590. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19487381>

45. Yang JC, Sherry RM, Steinberg SM, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. *J Clin Oncol* 2003;21:3127-3132. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12915604>
46. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 2002;20:289-296. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11773181>
47. Leibovich BC, Blute ML, Cheville JC, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer* 2003;97:1663-1671. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12655523>
48. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356:115-124. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17215529>
49. Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006;24:16-24. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16330672>
50. Chow LQ and Eckhardt SG. Sunitinib: from rational design to clinical efficacy. *J Clin Oncol* 2007;25:884-896. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17327610>
51. Faivre S, Delbaldo C, Vera K, et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol* 2006;24:25-35. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16314617>
52. Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. *Lancet Oncol* 2009;10:757-763. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19615940>
53. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007;370:2103-2111. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18156031>
54. Rini BI, Choueiri TK, Elson P, et al. Sunitinib-induced macrocytosis in patients with metastatic renal cell carcinoma. *Cancer* 2008;113:1309-1314. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18618496>
55. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol* 2010;28:2137-2143. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20368558>
56. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010;28:1061-1068. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20100962>
57. 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. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17538086>
58. Awada A, Hendlisz A, Gil T, et al. Phase I safety and pharmacokinetics of BAY 43-9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumours. *Br J Cancer* 2005;92:1855-1861. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15870716>
59. Clark JW, Eder JP, Ryan D, et al. Safety and pharmacokinetics of the dual action Raf kinase and vascular endothelial growth factor receptor inhibitor, BAY 43-9006, in patients with advanced, refractory



solid tumors. Clin Cancer Res 2005;11:5472-5480. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16061863>

60. Moore M, Hirte HW, Siu L, et al. Phase I study to determine the safety and pharmacokinetics of the novel Raf kinase and VEGFR inhibitor BAY 43-9006, administered for 28 days on/7 days off in patients with advanced, refractory solid tumors. Ann Oncol 2005;16:1688-1694. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16006586>

61. Strumberg D, Richly H, Hilger RA, et al. Phase I clinical and pharmacokinetic study of the Novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. J Clin Oncol 2005;23:965-972. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15613696>

62. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004;64:7099-7109. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15466206>

63. Escudier B, Szczylik C, Hutson TE, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon alfa-2a in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:1280-1289. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19171708>

64. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449-456. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18653228>

65. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. Cancer 2010;116:4256-4265. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20549832>

66. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125-134. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17215530>

67. Eisen T, Bukowski RM, Staehler M, et al. Randomized phase III trial of sorafenib in advanced renal cell carcinoma (RCC): Impact of crossover on survival [abstract]. J Clin Oncol (Meeting Abstracts) 2006;24:Abstract 4524. Available at http://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/4524

68. Bukowski RM, Eisen T, Szczylik C, et al. Final results of the randomized phase III trial of sorafenib in advanced renal cell carcinoma: Survival and biomarker analysis [abstract]. J Clin Oncol (Meeting Abstracts) 2007;25:Abstract 5023. Available at http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/5023

69. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006;295:2516-2524. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16757724>

70. Dudek AZ, Zolnierek J, Dham A, et al. Sequential therapy with sorafenib and sunitinib in renal cell carcinoma. Cancer 2009;115:61-67. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19051290>

71. Eichelberg C, Heuer R, Chun FK, et al. Sequential use of the tyrosine kinase inhibitors sorafenib and sunitinib in metastatic renal cell carcinoma: a retrospective outcome analysis. Eur Urol 2008;54:1373-1378. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18692304>

72. Heuer R, Eichelberg C, Zacharias M and Heinzer H. Sequential use of the tyrosine kinase inhibitors sorafenib and sunitinib [abstract]. Eur Urol 2009;Suppl 8(4):183 Abstract 251. Available at [http://www.european-urology.eu/article/S1569-9056\(09\)60257-8/fulltext](http://www.european-urology.eu/article/S1569-9056(09)60257-8/fulltext)

73. Sablin MP, Bouaita L, Balleyguier C, et al. Sequential use of sorafenib and sunitinib in renal cancer: Retrospective analysis in 90 patients [abstract]. J Clin Oncol 2007;25:Abstract 5038. Available at http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/5038

74. Sablin MP, Negrier S, Ravaud A, et al. Sequential sorafenib and sunitinib for renal cell carcinoma. J Urol 2009;182:29-34; discussion 34. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19447417>

75. Shepard DR, Rini BI, Garcia JA, et al. A multicenter prospective trial of sorafenib in patients (pts) with metastatic clear cell renal cell carcinoma (mccRCC) refractory to prior sunitinib or bevacizumab [abstract]. J Clin Oncol 2008;26:Abstract 5123. Available at http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/5123

76. Zimmermann K, Schmittel A, Steiner U, et al. Sunitinib treatment for patients with advanced clear-cell renal-cell carcinoma after progression on sorafenib. Oncology 2009;76:350-354. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19321976>

77. Dutcher JP, de Souza P, McDermott D, et al. Effect of temsirolimus versus interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumor histologies. Med Oncol 2009;26:202-209. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19229667>

78. Gordon MS, Hussey M, Nagle RB, et al. Phase II study of erlotinib in patients with locally advanced or metastatic papillary histology renal cell cancer: SWOG S0317. J Clin Oncol 2009;27:5788-5793. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19884559>

79. Dutcher JP and Nanus D. Long-term survival of patients with sarcomatoid renal cell cancer treated with chemotherapy. Med Oncol 2010. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20717755>

80. Nanus DM, Garino A, Milowsky MI, et al. Active chemotherapy for sarcomatoid and rapidly progressing renal cell carcinoma. Cancer 2004;101:1545-1551. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15378501>

81. Haas N, Manola J, Pins M, Liu G, McDermott D, Nanus D, Heath E, Wilding G, Dutcher J. . ECOG 8802: Phase II trial of doxorubicin (Dox) and gemcitabine (Gem) in metastatic renal cell carcinoma (RCC) with sarcomatoid features [abstract]. ASCO

Genitourinary Cancers Symposium 2009;Abstract 285 Available at http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=64&abstractID=20250

82. Lipton A, Zheng M and Seaman J. Zoledronic acid delays the onset of skeletal-related events and progression of skeletal disease in patients with advanced renal cell carcinoma. Cancer 2003;98:962-969. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12942563>

83. Rosen LS, Gordon D, Tchekmedyan NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. Cancer 2004;100:2613-2621. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15197804>