National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Kidney Cancer

NCCN Evidence Blocks™

Version 2.2020 — August 5, 2019

NCCN.org

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Kidney Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

*Robert J. Motzer, MD/Chair † Þ
Memorial Sloan Kettering Cancer Center

*Eric Jonasch, MD/Vice-chair †
The University of Texas
MD Anderson Cancer Center

Neeraj Agarwal, MD ‡ †
Huntsman Cancer Institute
at the University of Utah

Ajjai Alva, MBBS †
University of Michigan Rogel Cancer Center

Sam Bhayani, MD ω
Siteman Cancer Center at Barnes-Jewish Hospital
and Washington University School of Medicine

Toni K. Choueiri, MD † Þ
Dana-Farber/Brigham and Women's Cancer Center

Brian A. Costello, MD, MS †
Mayo Clinic Cancer Center

Ithaar H. Derweesh, MD ω
UC San Diego Moores Cancer Center

Thomas H. Gallagher, MD Þ
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

Saby George, MD †
Roswell Park Comprehensive Cancer Center

John L. Gore, MD, MS ω
Fred Hutchinson Cancer Research Center/Seattle
Cancer Care Alliance

Naomi Haas, MD †
Abramson Cancer Center
at the University of Pennsylvania

Steven L. Hancock, MD § Þ
Stanford Cancer Institute

Michael R. Harrison, MD †
Duke Cancer Institute

Christos Kyriakopoulos, MD ‡
University of Wisconsin Carbone Cancer Center

Chad LaGrange, MD ω
Fred & Pamela Buffett Cancer Center

Elaine T. Lam, MD †
University of Colorado Cancer Center

Clayton Lau, MD ω
City of Hope National Medical Center

Bryan Lewis ¥
Kidney Cancer Coalition

Brandon Manley, MD ω
Moffitt Cancer Center

Brittany McCreery, MD, MBA
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

Andrew McDonald, MD, MS §
O'Neal Comprehensive Cancer Center at UAB

M. Dror Michaelson, MD, PhD †
Massachusetts General Hospital Cancer Center

Amir Mortazavi, MD †
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Lakshminarayanan Nandagopal, MD †
O'Neal Comprehensive Cancer Center at UAB

Phillip M. Pierorazio, MD ω
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Elizabeth R. Plimack, MD, MS † Þ
Fox Chase Cancer Center

Lee Ponsky, MD ω
Case Comprehensive Cancer Center/University
Hospitals Seidman Cancer Center and
Cleveland Clinic Taussig Cancer Institute

Bruce G. Redman, DO †
University of Michigan Rogel Cancer Center

Bradley Somer, MD † ‡
St. Jude Children's Research Hospital/The
University of Tennessee Health Science Center

Jeffrey Sosman, MD ‡
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Geoffrey Wile, MD §
Vanderbilt-Ingram Cancer Center

NCCN
Mary Dwyer, MS
Lydia Hammond, MBA
Griselda Zuccarino-Catania, PhD

NCCN Guidelines Panel Disclosures

Continue

‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology
¥ Patient advocacy
§ Radiotherapy/Radiation oncology
ω Urology
*Discussion writing committee member

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Kidney Cancer
NCCN Evidence Blocks™

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

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

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

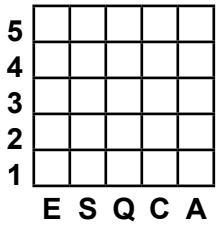
See NCCN Categories of Preference

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Kidney Cancer
NCCN Evidence Blocks™

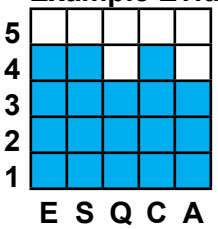
NCCN Guidelines Index
Table of Contents
Discussion

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

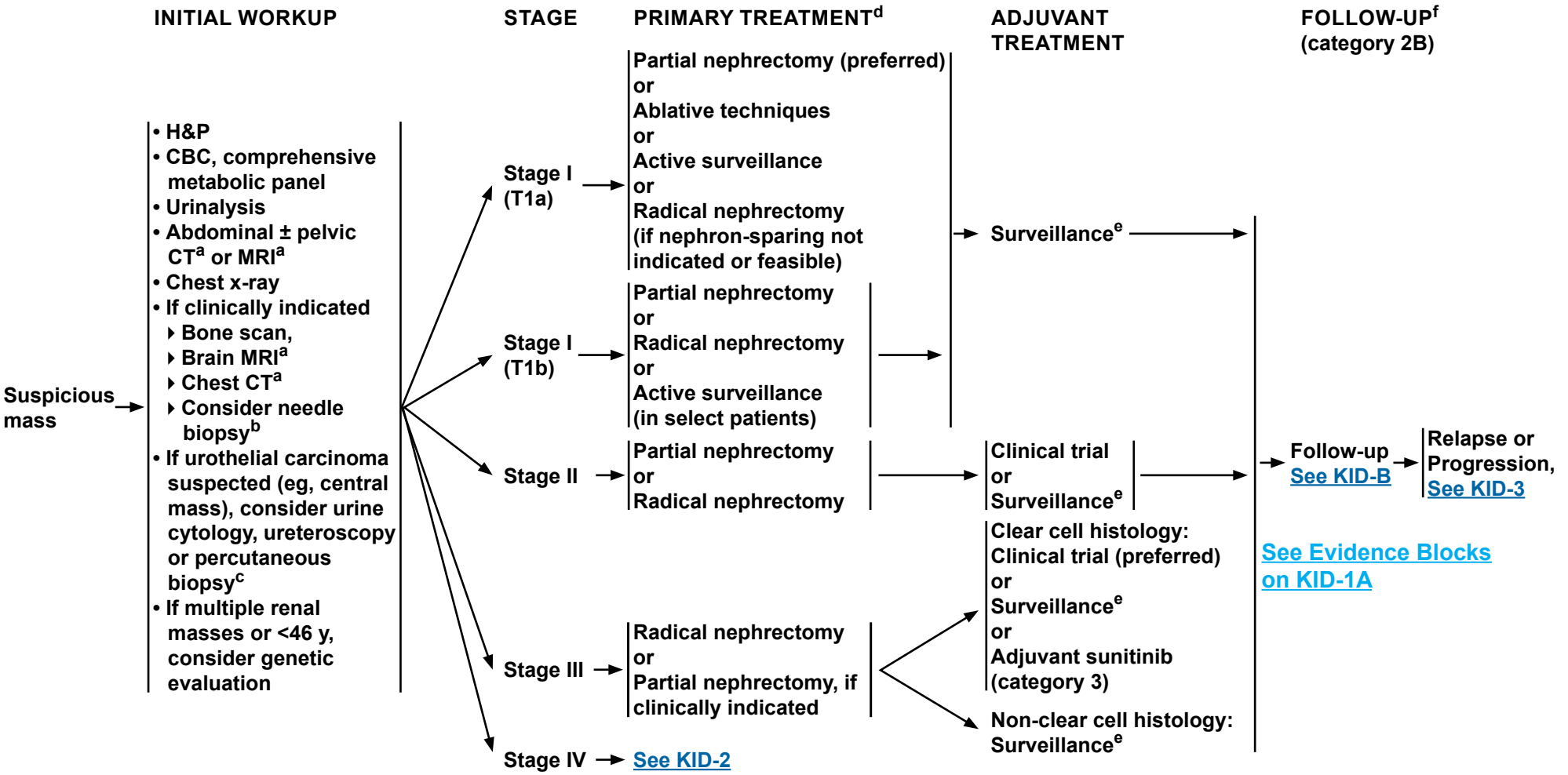
Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Kidney Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion



[a] Contrast is strongly preferred, such as a renal protocol.
[b] Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance or ablative techniques, cryosurgery, and radiofrequency ablation strategies.
[c] If metastatic disease is present or the patient cannot tolerate ureteroscopy.
[d] See Principles of Surgery (KID-A).
[e] See Follow-up (KID-B).
[f] No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

EVIDENCE BLOCKS FOR SYSTEMIC ADJUVANT TREATMENT FOLLOWING NEPHRECTOMY FOR CLEAR CELL HISTOLOGY AND HIGH–RISK RENAL CELL CARCINOMA

Sunitinib	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

STAGE | **PRIMARY TREATMENT[d]**

Stage IV

- **Potentially surgically resectable primary[g]** → **Consider tissue sampling** →
  - **Cytoreductive nephrectomy in select patients** → **See KID-3**
  - **or**
  - **Systemic therapy (See KID-3) (preferred in clear cell histology with poor-risk features)**
- **Surgically unresectable[g]** → **Tissue sampling** → **See KID-3**

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

RELAPSE OR STAGE IV

	TREATMENT		DISEASE PROGRESSION
Clear cell histology	Clinical trial or See First-Line Therapy (KID-C, 1 of 2) or Metastasectomy or SBRT or ablative techniques for oligometastatic disease and Best supportive care[h]	→ Follow-up See KID-B →	Clinical trial or See Subsequent Therapy for Clear Cell Histology (KID-C, 1 of 2) and Best supportive care[h]
Non-clear cell histology	Clinical trial (preferred) or See Systemic Therapy (KID-C, 2 of 2) or Metastasectomy or SBRT or ablative techniques for oligometastatic disease and Best supportive care[h]	→ Follow-up See KID-B →	Clinical trial or See Systemic Therapy for Non-Clear Cell Histology (KID-C, 2 of 2) and Best supportive care[h]

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SURGERY

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

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

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

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

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

- Thermal ablation (eg, cryosurgery, radiofrequency ablation) is an option for the management of patients with clinical stage T1 renal lesions.
  - Thermal ablation is an option for masses <3 cm, but may also be an option for larger masses in select patients. Ablation in masses >3 cm is associated with higher rates of local recurrence/persistence and complications.
  - Biopsy of small lesions confirms a diagnosis of malignancy for surveillance, cryosurgery, and radiofrequency ablation strategies.
  - Ablative techniques are associated with a higher local recurrence rate than conventional surgery and may require multiple treatments to achieve the same local oncologic outcomes.[a,b]

- Active surveillance is an option for the initial management of patients with clinical stage T1 renal lesions, for example:
  - Patients with small renal masses <2 cm given the high rates of benign tumors and low metastatic potential of these masses.
  - Active surveillance of patients with T1a tumors (≤4 cm) that have a predominantly cystic component is recommended.
  - Patients with clinical stage T1 masses and significant competing risks of death or morbidity from intervention.
  - Active surveillance entails serial abdominal imaging with timely intervention should the mass demonstrate changes (eg, increasing tumor size, growth rate, infiltrative pattern) indicative of increasing metastatic potential.
  - Active surveillance should include periodic metastatic survey including blood work and chest imaging, particularly if the mass demonstrates growth.

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

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

Stage I (T1a)

Follow-up During Active Surveillance[c]

- **H&P annually**
- **Laboratory tests annually, as clinically indicated**
- **Abdominal imaging:**
  - **Abdominal CT or MRI with contrast if no contraindication within 6 mo of surveillance initiation, then CT, MRI, or US at least annually**
- **Chest imaging:**
  - **Chest x-ray or CT at baseline and annually as clinically indicated to assess for pulmonary metastases**
- **Consider renal mass biopsy at initiation of active surveillance or at follow-up, as clinically indicated**
- **Follow-up may be individualized based on surgical status, treatment schedules, side effects, comorbidities, and symptoms**

Follow-up After Ablative Techniques[c]

- **H&P annually**
- **Laboratory tests annually, as clinically indicated**
- **Abdominal imaging:**
  - **Abdominal CT or MRI at 3–6 mo following ablative therapy unless otherwise contraindicated then CT or MRI (preferred), or US annually for 5 y or longer as clinically indicated**
  - **If there is imaging or clinical concerns for recurrence, then more frequent imaging, renal mass biopsy, or further treatment may be indicated.**
- **Chest imaging:**
  - **Chest x-ray or CT annually for 5 y for patients who have biopsy-proven low-risk RCC, nondiagnostic biopsies, or no prior biopsy**

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

Stage I (pT1a) and (pT1b)[c]

Follow-up After a Partial or Radical Nephrectomy

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

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

Follow-up for Stage II or III

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

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLLOW-UP
(category 2B)

Follow-up after Adjuvant Therapy

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

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

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

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLLOW-UP
(category 2B)

Long Term Follow-Up (>5 y)

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

REFERENCES

Active Surveillance

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

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

Kassiri B, Cheaib JG, Pierorazio PM. Patients with small renal masses undergoing active surveillance: Is yearly chest imaging necessary? J Urol 2019 Jan 31. [Epub ahead of print].

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

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

Ablation

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

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

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

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

Locally Advanced Disease

Gershman B, Moreira DM, Thompson RH, et al. Renal cell carcinoma with isolated lymph node involvement: Long-term natural history and predictors of oncologic outcomes following surgical resection. Eur Urol 2017 Aug;72(2):300-306.

Long Term Follow-Up

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

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

Dabestani S, Beisland C, Stewart GD, et al. Long-term outcomes of follow-up for initially localised clear cell renal cell carcinoma: RECUR database analysis. Eur Urol Focus 2018 Mar 7. [Epub ahead of print]

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

See Evidence Blocks on KID-C (EB-1)

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred regimens	Other recommended regimens	Useful under certain circumstances
Favorable[a]	• Axitinib + pembrolizumab • Pazopanib • Sunitinib	• Ipilimumab + nivolumab • Cabozantinib (category 2B) • Axitinib + avelumab	• Active surveillance[b] • Axitinib (category 2B) • High-dose IL-2[c]
Poor/ intermediate[a]	• Ipilimumab + nivolumab (category 1) • Axitinib + pembrolizumab (category 1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab	• Axitinib (category 2B) • High-dose IL-2[c] • Temsirolimus[d]

See Evidence Blocks on KID-C (EB-2)

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

Preferred regimens	Other recommended regimens	Useful under certain circumstances
• Cabozantinib (category 1) • Nivolumab (category 1) • Ipilimumab + nivolumab	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab (category 3)	• Bevacizumab or biosimilar[e] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[c] (category 2B) • Temsirolimus[d] (category 2B)

[a] See Risk Models to Direct Treatment (IMDC criteria) (KID-D).
[b] Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol 2016;17:1317-1324.
[c] Patients with excellent performance status and normal organ function.
[d] The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium greater than 10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. 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.
[e] Biosimilar options include: bevacizumab-awwb, bevacizumab-bvzr.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

EVIDENCE BLOCKS FOR FIRST-LINE SYSTEMIC THERAPIES FOR CLEAR CELL CARCINOMA

FAVORABLE RISK PATIENTS	
Preferred regimens	
Axitinib/pembrolizumab	
Pazopanib	
Sunitinib	
Other recommended regimens	
Ipilimumab/nivolumab	
Cabozantinib	
Axitinib/avelumab	
Useful under certain circumstances	
Axitinib	
High dose IL-2	

POOR/INTERMEDIATE RISK PATIENTS	
Preferred regimens	
Ipilimumab/nivolumab	
Axitinib/pembrolizumab	
Cabozantinib	
Other recommended regimens	
Pazopanib	
Sunitinib	
Axitinib/avelumab	
Useful under certain circumstances	
Axitinib	
High dose IL-2	
Temsirolimus (poor-prognosis group)	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

EVIDENCE BLOCKS FOR SUBSEQUENT SYSTEMIC THERAPIES FOR CLEAR CELL CARCINOMA

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY	
Preferred regimens	
Cabozantinib	
Nivolumab	
Ipilimumab/nivolumab	
Other recommended regimens	
Axitinib	
Lenvatinib/everolimus	
Axitinib/pembrolizumab	
Everolimus	
Pazopanib	
Sunitinib	
Axitinib/avelumab	
Useful under certain circumstances	
Bevacizumab	
Bevacizumab-awwb	
Sorafenib	
High-dose IL-2 for selected patients	
Temsirolimus	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[f]

Preferred regimens	Other recommended regimens	Useful under certain circumstances
• Clinical trial • Sunitinib	• Cabozantinib • Everolimus	• Axitinib • Bevacizumab or biosimilar[e] • Erlotinib • Lenvatinib + everolimus • Nivolumab • Pazopanib • Bevacizumab or biosimilar[e] + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC) • Bevacizumab or biosimilar[e] + everolimus • Temsirolimus[d] (category 1 for poor-prognosis risk group; category 2A for other risk groups)

See Evidence Blocks on KID-C (EB-3)

[d] The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium greater than 10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. 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.

[e] Biosimilar options include: bevacizumab-awwb, bevacizumab-bvzr.

[f] For collecting duct or medullary subtypes, partial responses have been observed with cytotoxic chemotherapy (carboplatin + gemcitabine, carboplatin + paclitaxel, or cisplatin + gemcitabine) and other platinum-based chemotherapies currently used for urothelial carcinomas. Oral targeted therapies generally do not produce responses in patients with renal medullary carcinoma. Outside of clinical trials, platinum-based chemotherapy regimens should be the preferred therapy for renal medullary carcinoma.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

EVIDENCE BLOCKS FOR SYSTEMIC THERAPIES FOR NON-CLEAR CELL CARCINOMA

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY	
Preferred regimens	
Sunitinib	
Other recommended regimens	
Cabozantinib	
Everolimus	
Useful under certain circumstances	
Axitinib	
Bevacizumab	
Bevacizumab-awwb	
Erlotinib	
Lenvatinib/everolimus	
Nivolumab	
Pazopanib	
Bevacizumab/erlotinib	
Bevacizumab-awwb/erlotinib	
Bevacizumab/everolimus	
Bevacizumab-awwb/everolimus	
Temsirolimus (poor-prognosis risk)	
Temsirolimus (risk groups other than poor-risk)	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

RISK MODELS TO DIRECT TREATMENT

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

Prognostic factors

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

Prognostic risk groups

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

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

Prognostic factors

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

Prognostic risk groups

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

[a] Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 2002;20:289-296.

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

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

Table 2. **AJCC Prognostic Groups**

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

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

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

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

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Discussion

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

Table of Contents

Overview

An estimated 73,820 Americans will be diagnosed with cancers of the kidney and renal pelvis and 14,770 will die of the disease in the United States in 2019.[1] Renal cell carcinoma (RCC) comprises approximately 3.8% of all new cancers, with a median age at diagnosis of 64 years.[2] Approximately 85% of kidney tumors are RCC, and approximately 70% of these have a clear cell histology.[3-5] Other less common cell types include papillary, chromophobe, translocation, and Bellini duct (collecting duct) tumors. Medullary renal carcinoma is a rare and aggressive RCC variant that almost exclusively arises in patients who are sickle-cell trait positive.[6]

Smoking, obesity, and hypertension are established risk factors for RCC development. Several hereditary types of RCC also exist, with von Hippel-Lindau (VHL) disease being the most common. VHL disease is caused by an autosomal-dominant constitutional mutation in the *VHL* gene that predisposes to clear cell RCC and other proliferative vascular lesions.[7-10] Analysis of the SEER database indicates that RCC incidence has been rising on average 0.6% each year and death rates have been falling on average 0.7% each year from 2006 through 2015.[2] The 5-year survival for localized RCC has increased from 88.4% (during 1992–1995) to 92.6% (during 2007–2013) and for advanced disease from 7.3% (during 1992–1995) to 11.7% (during 2007–2013).[11] The most important prognostic determinants of 5-year survival are the tumor stage, grade, local extent of the tumor, presence of regional nodal metastases, and evidence of metastatic disease at presentation.[12-21] RCC primarily metastasizes to the lung, bone, liver, lymph nodes, adrenal gland, and brain.[8,22,23]

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

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Kidney Cancer, an electronic search of the PubMed database was performed to obtain key literature in Kidney Cancer, published since the previous Guidelines update, using the following search terms: Renal Cell Carcinoma or Kidney Cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[24]

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

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

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

Initial Evaluation and Staging

Patients with RCC typically present with a suspicious mass involving the kidney that has been visualized using a radiographic study, often a CT scan. As the use of imaging methods (eg, abdominal CT with or without pelvic CT, ultrasound [US]) has become more widespread, the frequency of incidental detection of RCC has increased[25,26] and fewer patients present with the typical triad symptoms (hematuria, flank mass, and flank pain).

Less frequently, patients present with signs or symptoms resulting from metastatic disease, including bone pain, adenopathy, and pulmonary symptoms attributable to lung parenchyma or mediastinal metastases. Other presentations include fever, weight loss, anemia, or a varicocele. RCC in younger patients (≤46 years) may indicate an inheritable disorder,[27] and these patients should be referred to a hereditary cancer clinic for further evaluation.

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

CT of the abdomen with or without pelvic CT and chest x-ray are essential studies in the initial workup.[28] For metastatic evaluation, at the very least, chest radiography must be performed, although chest CT is more accurate than chest radiograph for chest staging.[29,30] Abdominal MRI is used to evaluate the inferior vena cava if tumor involvement is suspected, or it can be used instead of CT for detecting renal masses and for staging when contrast material cannot be administered because of allergy or moderate renal insufficiency.[31,32] All imaging studies should be performed with contrast, such as renal protocol.

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

Most bone and brain metastases are symptomatic at diagnosis. Therefore, a bone scan is not routinely performed unless the patient has an elevated serum alkaline phosphatase (ALP) or complains of bone pain.[33] CT or MRI of the brain can be performed if clinical signs, presentation, and symptoms suggest brain metastases.

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

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

The use of current TNM classification[36] and classification of histologic subtypes[37] are important in making treatment decisions.

Treatment of Localized Disease

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

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

Nephron-Sparing Surgery and Radical Nephrectomy

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

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

Partial nephrectomy has well-established oncologic outcomes data comparable to radical nephrectomy.[46-51] Radical nephrectomy can lead to an increased risk for chronic kidney disease[52,53] and is associated with increased risks of cardiovascular morbidity and mortality according to population-based studies.[54] When compared with radical nephrectomy, partial nephrectomy can achieve preserved renal function, decreased overall mortality, and reduced frequency of cardiovascular events.[54-58] Patients with a hereditary form of RCC, such as VHL disease, should also be considered for nephron-sparing therapy. Nephron-sparing surgery has been used increasingly in patients with T1a and T1b renal tumors (ie, up to 7 cm in greatest dimension) and a normal contralateral kidney, with equivalent outcomes to radical nephrectomy.[49,59-61] Radical nephrectomy should not be employed when nephron sparing can be achieved. A more recent study showed that among Medicare beneficiaries with early-stage kidney cancer, treatment with partial rather than radical nephrectomy was associated with improved survival.[62]

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

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

Lymph Node Dissection

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

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

Adrenalectomy

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

Active Surveillance and Ablative Techniques

Active surveillance[74,75] is defined as the initial monitoring of tumors using abdominal imaging techniques with delayed intervention when indicated. Elderly patients and those with small renal masses (<2 cm) and other comorbidities often have a low RCC-specific mortality.[76] Active surveillance and ablative techniques such as cryo- or radiofrequency ablation are alternative strategies for selected patients, particularly the elderly and those with competing health risks.

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

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

Management of Stage I (T1a) Disease

The NCCN Panel prefers surgical excision by partial nephrectomy for the management of clinical stage I (T1a) renal masses. Adequate expertise and careful patient selection are important. Partial nephrectomy is most appropriate in patients with small unilateral tumors or whenever preservation of renal function is a primary issue, such as in patients having one kidney or those with renal insufficiency, bilateral renal masses, or familial RCC. Both open and laparoscopic approaches to partial nephrectomy can be considered, depending on tumor size, location, and the surgeon's expertise.

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

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

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

The NCCN Guidelines recommend active surveillance and ablative techniques only in selected patients with stage I (T1a) RCC.

Management of Stage I (T1b) Disease

Partial nephrectomy for localized RCC has an oncologic outcome similar to that of radical surgery for T1b tumors.[81,82] Surgery by partial nephrectomy, whenever feasible, or by radical nephrectomy is the

standard of care for clinical T1b tumors according to the NCCN Kidney Cancer Panel.

Management of Stage II and III Disease

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

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

Adjuvant Treatment for Clear Cell, High-Risk Localized RCC

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

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

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

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

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

Follow-up After Treatment of Localized Disease

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

The NCCN Panel has provided a framework for follow-up of patients undergoing surveillance of a small renal mass and for patients who underwent surgery or ablative therapy of a primary RCC. The NCCN Panel has reiterated in a footnote that no single follow-up plan is appropriate for everyone, and follow-up should be modified for the individual patient using clinical judgment. Since uniform consensus among the panel members regarding the most appropriate follow-up plan is lacking, these recommendations are listed as category 2B. Also, the guidance for follow-up has been provided for the first 5 years after nephrectomy, with follow-up evaluation to be extended beyond 5 years at the discretion of the physician. Results from a retrospective analysis indicate that in a subset of patients, relapses occur more than 5 years after surgery for their primary RCC.[90] The analysis suggests that continued follow-up/surveillance after 5 years may be of potential value in some patients. Another retrospective analysis suggests that patients with lower risk are more likely to relapse later.[91] Identification of subsets of patients with higher risk who require longer follow-up has not been defined, and further research is required to refine follow-up strategies for patients with RCC.

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

Follow-up During Active Surveillance for Stage T1a

For follow-up during active surveillance, the NCCN Panel recommends a history and physical examination, a comprehensive metabolic panel, and other tests every 6 months for 2 years and then annually for up to 5 years after diagnosis. In order to study the growth rate of the tumor, the NCCN Panel recommends abdominal imaging (with CT or MRI) within 6 months for 2 years from initiation of active surveillance; subsequent imaging (with CT, MRI, or US) may be performed annually thereafter. All three modalities (US, CT, and MRI) have been found to accurately predict pathologic tumor size in a retrospective analysis.[92] Therefore, best clinical judgment should be used in choosing the imaging modality. For patients with biopsy positive for RCC, the recommendation is to annually assess for pulmonary metastases using chest imaging techniques (chest x-ray or chest CT). The panel recommends imaging of the pelvis; CT or MRI of the head or spine, if there are neurologic symptoms; or bone scan in cases of elevated ALP, bone pain, or abnormal radiologic findings.

Follow-up After Ablative Therapy for Stage T1a

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

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

Follow-up After Nephrectomy for Stages I–III

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

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

For patients with stage II–III after radical nephrectomy, larger tumors have a substantially higher risk of both local and metastatic recurrence; therefore, an increased frequency of examinations is recommended compared with patients with stages pT1a or pT1b. The NCCN Panel recommends a history and physical examination every 3 to 6 months for 3 years, then annually for 5 years after radical nephrectomy. The follow-up evaluation may be extended beyond 5 years at the discretion of the physician as clinically indicated. A comprehensive metabolic panel and other tests are recommended as clinically indicated every 6 months for 2 years, then annually for 5 years after radical nephrectomy, and thereafter as clinically indicated.

The panel recommends baseline chest imaging (with CT) and abdominal scans (CT or MRI) within 3 to 6 months following surgery with continued imaging (chest CT; CT, MRI, or US of the abdomen) every 6 months for at least 3 years, and annually thereafter for up to 5 years after radical nephrectomy.[95] While the use of US imaging for follow-up is an option for low-risk patients, CT is the preferred modality for those with a high risk of recurrence. There is disagreement among the panel members regarding the usefulness of US in patients with stage III disease; therefore, it is listed as a category 2B option specifically for patients with stage II disease. The panel has noted that imaging beyond 5 years may be performed as clinically indicated, and site-specific imaging may be performed as symptoms warrant. Other tests such as imaging of the pelvis, CT or MRI of the head or spine, or bone scan are recommended as clinically indicated.

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

Management of Relapsed or Stage IV Disease

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

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

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

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

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

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

Systemic Therapy Options for Patients with Relapsed or Stage IV Disease

The cytokine era introduced IFN-α and high-dose IL-2 as therapies for RCC, which are now only used in selected patients. Targeted therapy utilizing tyrosine kinase inhibitors (TKIs), and/or anti-VEGF antibodies, is now widely used in first- and second-line treatments. Agents targeting the mammalian target of rapamycin (mTOR) are also used in this setting. A number of targeted agents have been approved by the FDA for the

treatment of advanced RCC in the first and/or subsequent lines of therapy: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus, bevacizumab in combination with interferon, cabozantinib, and lenvatinib (plus everolimus). Immune checkpoint inhibitors are the new revolution in treatment options. Checkpoint antibodies alter the interaction between immune cells and antigen-presenting cells, including tumor cells. These agents can augment an anti-tumor immune response and have shown promise in a number of tumor indications. Recent studies have shown efficacy of nivolumab checkpoint monotherapy in the second-line setting for patients with advanced RCC and the combination of nivolumab and ipilimumab in the first-line setting.

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

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

Prognostic Models

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

The most widely used prognostic factor model is from the Memorial Sloan Kettering Cancer Center (MSKCC). The model was derived from examining prognostic factors in patients (n = 463) with metastatic RCC enrolled in clinical trials and treated with IFN.[105] Prognostic factors for multivariable analysis included five variables: interval from diagnosis to treatment of less than 1 year; Karnofsky performance status less than 80%; serum lactate dehydrogenase (LDH) greater than 1.5 times the upper limit of normal (ULN); corrected serum calcium greater than the ULN; and serum hemoglobin less than the lower limit of normal (LLN). Patients with none of these factors are considered low risk or with good prognosis, those with 1 or 2 factors present are considered intermediate risk, and patients with 3 or more of the factors are considered poor risk. The MSKCC criteria have been additionally validated by an independent group at the Cleveland Clinic.[107]

A prognostic model derived from a population of patients with metastatic RCC treated with VEGF-targeted therapy has been developed, and is known as the IMDC or Heng’s model.[106] This model was derived from a retrospective study of 645 patients with metastatic RCC treated with sunitinib, sorafenib, or bevacizumab plus interferon. Patients who received prior immunotherapy (ie, received their targeted therapy as second-line treatment) also were included in the analysis. The analysis identified six clinical parameters to stratify patients into favorable, intermediate, and poor prognosis groups. Four of the five adverse prognostic factors are those previously identified by MSKCC as independent predictors of short survival: hemoglobin less than the LLN, serum-corrected calcium greater than the ULN, Karnofsky performance status less than 80%, and time from

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

Patients with none of the identified six adverse factors were in the favorable-risk category (n = 133; 22.7%) in which a median OS was not reached and a 2-year OS was 75% (95% CI, 65%–82%). Patients with one or two adverse factors were in the intermediate-risk category (n = 301; 51.4%) in which a median OS was 27 months and a 2-year OS was 53% (95% CI, 46%–59%). Finally, those patients with three to six adverse factors were in the poor-risk category (n = 152; 25.9%) in which a median OS was 8.8 months and a 2-year OS was 7% (95% CI, 2%–16%).[106] This model was validated in an independent dataset.[108]

First-line Therapy for Patients with Clear Cell RCC

Pazopanib as First-line Therapy for Clear Cell RCC

Pazopanib is an oral angiogenesis inhibitor targeting VEGF receptors (VEGFR-1, -2, and -3), platelet-derived growth factor receptors (PDGFR-α and –β), and stem cell factor receptor (c-KIT). The safety and effectiveness of pazopanib were evaluated in a phase III, open-label, international, multicenter study. Four hundred thirty-five patients with clear cell advanced RCC and measurable disease with no prior treatment or 1 prior cytokine-based treatment were randomized 2:1 to pazopanib or placebo. PFS was prolonged significantly with pazopanib in the overall study population, averaging 9.2 months versus 4.2 months for patients assigned to placebo.[109] The treatment-naive subpopulation of 233 patients, randomized 2:1 to pazopanib versus placebo, had a median PFS of 11.1 months on pazopanib versus 2.8 months on placebo.[109] The overall response rate (ORR) was 30% with pazopanib and 3% with placebo (all results were statistically significant). Common adverse reactions to pazopanib (any grade) included diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting, fatigue, weakness, abdominal pain, and headache. Notable grade 3 toxicity was hepatotoxicity, indicated by elevated levels of alanine (30%) and aspartate (21%) transaminase. Therefore, it is critical to monitor liver function before and during treatment with the drug.

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

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

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

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

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

Sunitinib as First-line Therapy for Clear Cell RCC

Sunitinib is a multikinase inhibitor targeting several receptor tyrosine kinases, including PDGFR-α and -β; VEGFR-1, -2, and -3; c-KIT; FMS-like tyrosine kinase (FLT-3); colony-stimulating factor (CSF-1R); and neurotrophic factor receptor (RET).[114,115]

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

Updated results demonstrate a strong trend towards OS advantage of sunitinib over IFN-α in the first-line setting (26.4 months vs. 21.8 months, $P = .051$).[118] The OS based on pretreatment IMDC prognostic risk was not reached for patients in the favorable risk groups, but also had a trend towards OS advantage in the sunitinib over IFN-α arm for intermediate-risk (20.7 months vs. 15.4 months) and poor-risk groups (5.3 months vs. 4 months).[118] Results from an expanded access trial revealed that sunitinib possesses an acceptable safety profile and has activity in subgroups of patients with brain metastases, non-clear cell histology, and poor performance status.[119] Phase II studies using modified[120] or intermittent[121] sunitinib dosing schedules in patients with metastatic RCC showed high efficacy and lower toxicity.

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

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

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

Nivolumab is an antibody that selectively blocks the interaction between programmed death-1 (PD-1; expressed on activated T cells) and its ligands (expressed on antigen-presenting cells, including immune cells and tumor cells). Ipilimumab is an antibody that selectively blocks the interaction between the negative regulator cytotoxic T-lymphocyte antigen 4 (CTLA-4; expressed early on activated T cells) and its ligands CD80/CD86 (expressed on antigen-presenting cells).

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

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

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

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

Cabozantinib as First-line Therapy for Clear Cell RCC

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

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

Active Surveillance for Select, Asymptomatic Patients with Clear Cell RCC

A subset of patients with advanced RCC show indolent progression of disease and could benefit from initial active surveillance because of the toxicity and non-curative nature of systemic therapies. A prospective phase II trial of patients with treatment-naïve, asymptomatic, metastatic RCC followed patients on active surveillance through radiographic assessment at defined intervals until a decision was made to initiate systemic therapy.[126] Of the 48 patients included in the analysis, the median time of surveillance from registration to initiation of systemic therapy was 14.9 months. This study demonstrated that a subset of patients with advanced RCC can safely undergo active surveillance before starting systemic therapy. Therefore, the NCCN Panel included active surveillance as an option for select, asymptomatic patients with favorable-risk clear cell RCC.

Axitinib as First-line Therapy for Clear Cell RCC

Axitinib is a selective, second-generation inhibitor of VEGFR-1, -2, and -3.[127] As second-line therapy for patients with clear cell RCC, treatment with axitinib has clearly demonstrated greater ORR and longer median PFS compared with those treated with sorafenib. To determine whether this holds true in the first-line setting, a randomized, open-label, phase III trial was carried out in newly diagnosed patients randomized (2:1) to receive axitinib (5 mg twice daily) or sorafenib (400 mg twice daily).[128] The median PFS seen in patients treated with axitinib was 10.1 months (95% CI, 7.2–12.1) and for those treated with sorafenib was 6.5 months (95% CI, 4.7–8.3).[128] The adverse events more commonly seen with axitinib (≥10% difference) than with sorafenib treatment were diarrhea, hypertension, weight loss, decreased appetite, dysphonia, hypothyroidism, and upper abdominal pain; adverse events more commonly seen with sorafenib treatment included palmar-plantar erythrodysesthesia, rash, alopecia, and erythema.[128] The difference in PFS between patients treated with axitinib versus sorafenib is not statistically significant; however, the results demonstrated clinical activity of axitinib with acceptable toxicity profile in the first-line setting.

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

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

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

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

In the United States, a similar trial was performed by the Cancer and Leukemia Group B (CALGB), with 732 previously untreated patients randomized 1:1 to receive either IFN-α or the combination of bevacizumab plus IFN-α. Bevacizumab plus IFN-α produced a superior PFS (8.5 months vs. 5.2 months) and higher ORR (25.5% vs. 13.1%) versus IFN-α alone. However, toxicity was greater in the combination therapy arm.[131] There were no significant differences in median survival between the two groups (18.3 vs. 17.4 months for bevacizumab plus IFN-α vs. IFN-α alone).[132]

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

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

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

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

Temsirolimus as First-line Therapy for Clear Cell RCC

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

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

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

Subsequent Therapy for Patients with Clear Cell RCC

Cabozantinib as Subsequent Therapy for Clear Cell RCC

A phase III trial (METEOR) randomized 658 patients with disease progression after previous TKI therapy to receive 60 mg/d of oral cabozantinib (n = 331) or 10 mg/d of oral everolimus (n = 321).[139] The estimated median PFS for patients randomized to cabozantinib was 7.4 months, versus 3.8 months for everolimus (HR, 0.58; 95% CI, 0.45–0.75; $P < .001$). The ORR was 21% for cabozantinib and 5% for everolimus ($P < .001$).[139]

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

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

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

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

A network meta-analysis comparing the relative effectiveness of treatment options for RCC after failure of first-line therapy found the probability of longer PFS during the analyzed 3 years to be higher with cabozantinib compared to everolimus, nivolumab, axitinib, sorafenib, and best supportive care.[144]

Nivolumab as Subsequent Therapy for Clear Cell RCC

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

Treatment-related adverse events of any grade were seen in 79% of those who received nivolumab and 88% of those who received everolimus; grade 3-4 events occurred in 19% and 37%, respectively. The most common grade 3-4 events were fatigue (2%) with nivolumab and anemia (8%) with everolimus. Toxicities led to treatment discontinuations in 8% and 13% of patients, respectively. Two deaths were reported in the everolimus arm; there were no treatment-related deaths in the nivolumab arm.[145]

An independent analysis was carried out to determine the efficacy of nivolumab-based baseline factors such as number and location of metastases, risk group, number of prior therapies, and specific prior therapies (ie, sunitinib, pazopanib, IL-2). A consistent OS benefit and ORR were observed across all baseline factors.[146]

The FKSI-DRS[147] questionnaire was used to obtain a score for QOL of patients enrolled in the trial. The median change from baseline in the FKSI-DRS score in the nivolumab group increased over time, suggesting a significant and consistent improvement in QOL of patients in this group.[145] Due to the OS advantage shown by nivolumab over everolimus in the second-line setting, nivolumab is preferred over everolimus in the second-line setting for advanced RCC after an antiangiogenic agent.

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

Based on the results of the CheckMate 025 trial[145] demonstrating superior OS with nivolumab compared with everolimus, the NCCN Panel has included nivolumab as a category 1 preferred subsequent therapy option.

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

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

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

Axitinib as Subsequent Therapy for Clear Cell RCC

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

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

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

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

Lenvatinib with Everolimus as Subsequent Therapy for Clear Cell RCC

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

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

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

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

Everolimus as Subsequent Therapy for Clear Cell RCC

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

The primary objective of the phase II (RECORD-3) study was to assess non-inferiority of first-line everolimus compared with first-line sunitinib with respect to PFS and to determine the role of first-line mTOR inhibitor in metastatic RCC.[157] The median PFS after first-line sunitinib was 10.71 months compared with 7.85 months for everolimus. When patients progressed on first-line therapy, they were then crossed over to the alternative therapy and the combined PFS for the two sequences of treatment were also compared. The results indicated that the median PFS for patients treated with everolimus followed by sunitinib was 21.13 months compared with 25.79 months for those treated with sunitinib followed by everolimus (HR, 1.4; 95% CI, 1.2–1.8).[157] The median OS for first-line everolimus followed by sunitinib was 22.41 months compared with 32.03 months for first-line sunitinib followed by everolimus (HR, 1.2; 95% CI, 0.9–1.6).[157] The final OS analysis of RECORD-3 continues to support first-line sunitinib followed by everolimus (median OS was 29.5 months compared to 22.4 months for everolimus followed by sunitinib).[158]

Everolimus is listed as a category 2A, other recommended, subsequent therapy option in the NCCN Guidelines. It is important to note that two recent randomized phase III trials (discussed in sections above) compared the efficacy of everolimus with nivolumab and cabozantinib. The results of the CheckMate 025[145] trial demonstrated superior OS with nivolumab compared with everolimus. The METEOR trial[139] demonstrated longer PFS and OS with cabozantinib when compared to everolimus. Based on the results of these two phase III trials, eligible patients should preferentially receive either nivolumab or cabozantinib over everolimus.

Pazopanib as Subsequent Therapy for Clear Cell RCC

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

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

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

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

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

Sunitinib as Subsequent Therapy for Clear Cell RCC

Sunitinib also has demonstrated substantial anti-tumor activity in the second-line therapy of metastatic RCC after progression on cytokine therapy.[115,161] Studies investigating the sequential use of sunitinib and sorafenib mostly are retrospective. There are prospective data, although limited, that suggest a lack of total cross resistance between TKIs, either sorafenib followed by sunitinib failures or vice versa—an observation that is consistent with their differences in target specificities and slightly different toxicity spectra that sometimes permit tolerance of one agent over another.[162-166] Sunitinib is considered a category 2A, other recommended, subsequent therapy option.

Sorafenib as Subsequent Therapy for Clear Cell RCC

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

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

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

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

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

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

Other Agents as Subsequent Therapy for Clear Cell RCC

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

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

A phase II trial suggested benefit to temsirolimus therapy after prior treatment with a cytokine.[179] A phase III trial (INTORSECT) compared the efficacy of temsirolimus to sorafenib following first-line sunitinib as a treatment for patients with RCC.[180] The trial enrolled 512 patients with a performance status of 0 or 1 and either clear cell or non-clear cell histology. Patients were randomized to receive sorafenib at 400 mg twice daily or intravenous temsirolimus at 25 mg weekly. The difference in PFS, the primary endpoint of the trial, was not statistically significant (P = .1933) between the two arms. PFS was 4.28 months with temsirolimus compared to 3.91 months with sorafenib. A statistically significant OS advantage was observed for sorafenib. The median OS with temsirolimus was 12.27 months compared to 16.64 months with sorafenib (P = .0144).[180] However, the subgroup of individuals who had been treated with sunitinib for less than or equal to 180 days and were then treated with sorafenib did not show a survival benefit. Based on this study, in patients with a shortened response to first-line TKI, mTOR inhibition may be considered as second-line therapy.[181] The NCCN Panel considers temsirolimus a category 2B subsequent therapy option, useful under certain circumstances.

Systemic Therapy for Patients with Non-Clear Cell RCC

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

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

Sunitinib for Non-Clear Cell RCC

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

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

A meta-analysis of randomized clinical trials for patients with non-clear cell RCC found that treatment with TKIs reduced the risk of progression compared with mTOR inhibitors.[192] The study found sunitinib reduced the risk of progression compared to everolimus in the first-line setting (HR 0.67; 95% CI, 0.56–0.80; P < .00001). However, no significant differences between TKIs and mTOR inhibitors were found for OS and ORR.

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

Cabozantinib for Non-Clear Cell RCC

While no prospective trials have been done for cabozantinib in patients with non-clear cell RCC, a few retrospective studies[193,194] and real-world data reports[195] support its use as systemic therapy in this population. A retrospective study of 30 patients with non-clear cell RCC found clinical benefit for patients treated with cabozantinib.[193] The median PFS was 8.6 months and median OS was 25.4 months. The ORR was 14.3% among the 28 patients with measurable disease. The NCCN Panel included cabozantinib as a category 2A, other recommended option for patients with relapsed or stage IV, non-clear cell RCC.

Everolimus for Non-Clear Cell RCC

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

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

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

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

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

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

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

Pazopanib and Axitinib for Non-Clear Cell RCC

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

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

Bevacizumab Monotherapy for Non-Clear Cell RCC

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

Erlotinib for Non-Clear Cell RCC

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

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

Nivolumab for Non-Clear Cell RCC

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

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

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

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

Hereditary leiomyomatosis and RCC (HLRCC) is a hereditary condition in which affected patients are at risk for development of skin and uterine leiomyomas, as well as an aggressive form of papillary kidney cancer.[208] Bevacizumab in combination with either erlotinib or everolimus is currently being investigated for treatment of advanced papillary RCC, including HLRCC.

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

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

Bevacizumab + Everolimus for Advanced Non-Clear Cell RCC

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

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

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

Temsirolimus for Non-Clear Cell RCC

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

Randomized clinical trials in rarer subgroups of patients are often challenging. Consistent with the results of this phase III trial, a case report of a patient with a diagnosis of metastatic chromophobe RCC that was refractory to treatment with sunitinib achieved durable clinical response lasting 20 months upon treatment with temsirolimus.[212]

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

Chemotherapy for Metastatic RCC

Treatment of RCC with sarcomatoid features and non-clear cell histologies remains a challenge. Sarcomatoid variant is an aggressive form of RCC that can occur in any histologic subtype.[213] Sarcomatoid RCC is associated with a poor prognosis.[214-218] Chemotherapy plays a role in the management of a variety of sarcomas; therefore, its use in sarcomatoid RCC patients has been explored. Gemcitabine in combination with doxorubicin or in combination with capecitabine has shown some activity in patients with non-clear cell or clear cell tumors with sarcomatoid features.[219-224] The potential role of sunitinib in combination with gemcitabine has been investigated in a phase II trial of RCC with sarcomatoid features.[225] The role of bevacizumab in combination with capecitabine and gemcitabine has been studied in a phase II trial of sarcomatoid RCC with low response rates.[226] The results show that the combination was well tolerated and is active, especially in patients with rapidly progressing disease.[225] There are ongoing trials studying sunitinib in combination with gemcitabine compared to sunitinib alone in patients with sarcomatoid features.[227]

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

Collecting-duct carcinoma is also a very rare type of non-clear cell RCC, often presenting at an advanced stage of disease. Up to 40% of patients have metastatic spread at initial presentation, and most patients die within 1 to 3 years from the time of primary diagnosis.[231-234] Collecting duct carcinoma shares biologic features with urothelial carcinoma. In a multicenter prospective study, 23 patients with no prior therapy were treated with a combination of gemcitabine and either cisplatin or carboplatin.[235] The results showed a response rate of 26% and an OS of 10.5 months.[235]

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

Sorafenib is No Longer Recommended for Non-Clear Cell RCC

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

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

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

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

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

Supportive Care

Supportive care remains a mainstay of therapy for *all* patients with metastatic RCC (See NCCN Guidelines for Palliative Care). This includes surgery for patients with oligometastatic disease in the brain whose disease is well controlled extracranially. Stereotactic radiotherapy, if available, is an alternative to surgery for limited-volume brain metastasis, and whole brain irradiation is recommended for those patients with multiple brain metastases.[238]

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

Bone metastasis occurs in 30% to 40% of patients with advanced RCC.[239-241] Bone lesions in patients with RCC are typically osteolytic and cause considerable morbidity, leading to skeletal-related events (SREs), including bone pain with need for surgery or radiotherapy, hypercalcemia, pathologic fractures, and spinal cord compression. Two studies of patients with bone metastases showed an improvement in bone pain using different radiotherapy modalities.[242,243]

The role of bone-modifying agents such as bisphosphonates (eg, zoledronic acid) has been well established in this setting.[244,245] The newer bone-modifying agent approved for use in patients with RCC that has metastasized to the bone is the RANK-L inhibitor, denosumab. A phase III randomized trial directly compared the development of SREs on either denosumab or zoledronic acid in patients with multiple myeloma or bone metastases with a solid tumor (excluding breast or prostate cancer). The study enrolled 1776 patients with bone metastases from a wide range of cancer types, including patients with RCC (6%) not previously treated with a bisphosphonate.[246] Denosumab was reported to be non-inferior to zoledronic acid in delaying time to first on-study SRE (HR, 0.84; 95% CI, 0.71–0.98; *P* = .0007).[246]

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

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30620402.

2. SEER Stat Fact Sheets: Kidney and Renal Pelvis Cancer. Bethesda, MD: National Cancer Institute; Available at: http://seer.cancer.gov/statfacts/html/kidrp.html. Accessed November 9, 2018.

3. Moch H, Gasser T, Amin MB, et al. Prognostic utility of the recently recommended histologic classification and revised TNM staging system of renal cell carcinoma: a Swiss experience with 588 tumors. Cancer 2000;89:604-614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10931460.

4. Leibovich BC, Lohse CM, Crispen PL, et al. Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. J Urol 2010;183:1309-1315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20171681.

5. Lipworth L, Morgans AK, Edwards TL, et al. Renal cell cancer histological subtype distribution differs by race and sex. BJU Int 2016;117:260-265. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25307281.

6. Msaouel P, Hong AL, Mullen EA, et al. Updated Recommendations on the Diagnosis, Management, and Clinical Trial Eligibility Criteria for Patients With Renal Medullary Carcinoma. Clin Genitourin Cancer 2019;17:1-6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30287223.

7. 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.

8. DeVita VT Jr HS, Rosenberg SA. Cancer Principles and Practice of Oncology. (ed 8th). Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

9. Schmidt LS, Linehan WM. Genetic predisposition to kidney cancer. Semin Oncol 2016;43:566-574. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27899189.

10. DeVita VT Jr LT, Rosenberg SA. DeVita, Hellman, and Rosenberg's Cancer Principles and Practice of Oncology. (ed 10th). Philadelphia, PA: Wolters Kluwer Health; 2015.

11. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014, based on November 2016 SEER data submission, posted to the SEER web site, April 2017: National Cancer Institute. Bethesda, MD; 2017. Available at: https://seer.cancer.gov/csr/1975_2014/.

12. Ficarra V, Schips L, Guille F, et al. Multiinstitutional European validation of the 2002 TNM staging system in conventional and papillary localized renal cell carcinoma. Cancer 2005;104:968-974. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16007683.

13. Frank I, Blute ML, Leibovich BC, et al. Independent validation of the 2002 American Joint Committee on cancer primary tumor classification for renal cell carcinoma using a large, single institution cohort. J Urol 2005;173:1889-1892. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15879769.

14. Zisman A, Pantuck AJ, Chao D, et al. Reevaluation of the 1997 TNM classification for renal cell carcinoma: T1 and T2 cutoff point at 4.5 rather than 7 cm. better correlates with clinical outcome. J Urol 2001;166:54-58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11435822.

15. Klatte T, Patard JJ, Goel RH, et al. Prognostic impact of tumor size on pT2 renal cell carcinoma: an international multicenter experience. J Urol 2007;178:35-40; discussion 40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17521678.

16. Lam JS, Klatte T, Patard JJ, et al. Prognostic relevance of tumour size in T3a renal cell carcinoma: a multicentre experience. Eur Urol 2007;52:155-162. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17316970.

17. Minervini A, Lilas L, Minervini R, Selli C. Prognostic value of nuclear grading in patients with intracapsular (pT1-pT2) renal cell carcinoma. Long-term analysis in 213 patients. Cancer 2002;94:2590-2595. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12173325.

18. Dall'Oglio MF, Antunes AA, Sarkis AS, et al. Microvascular tumour invasion in renal cell carcinoma: the most important prognostic factor. BJU Int 2007;100:552-555. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17555475.

19. Dall'Oglio MF, Ribeiro-Filho LA, Antunes AA, et al. Microvascular tumor invasion, tumor size and Fuhrman grade: a pathological triad for prognostic evaluation of renal cell carcinoma. J Urol 2007;178:425-428; discussion 428. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17561167.

20. Lam JS, Shvarts O, Said JW, et al. Clinicopathologic and molecular correlations of necrosis in the primary tumor of patients with renal cell carcinoma. Cancer 2005;103:2517-2525. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15880379.

21. Sengupta S, Lohse CM, Leibovich BC, et al. Histologic coagulative tumor necrosis as a prognostic indicator of renal cell carcinoma aggressiveness. Cancer 2005;104:511-520. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15973740.

22. Bianchi M, Sun M, Jeldres C, et al. Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. Ann Oncol 2012;23:973-980. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21890909.

23. Meyer CP, Sun M, Karam JA, et al. Complications After Metastasectomy for Renal Cell Carcinoma-A Population-based Assessment. Eur Urol 2017;72:171-174. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28359734.

24. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html. Accessed July 24, 2014.

25. Jayson M, Sanders H. Increased incidence of serendipitously discovered renal cell carcinoma. Urology 1998;51:203-205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9495698.

26. Luciani LG, Cestari R, Tallarigo C. Incidental renal cell carcinoma-age and stage characterization and clinical implications: study of 1092 patients (1982-1997). Urology 2000;56:58-62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10869624.

27. Shuch B, Vourganti S, Ricketts CJ, et al. Defining early-onset kidney cancer: implications for germline and somatic mutation testing and clinical management. J Clin Oncol 2014;32:431-437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24378414.

28. Israel GM, Bosniak MA. How I do it: evaluating renal masses. Radiology 2005;236:441-450. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16040900.

29. Lim DJ, Carter MF. Computerized tomography in the preoperative staging for pulmonary metastases in patients with renal cell carcinoma. J Urol 1993;150:1112-1114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8371366.

30. Sheth S, Scatarige JC, Horton KM, et al. Current concepts in the diagnosis and management of renal cell carcinoma: role of multidetector ct and three-dimensional CT. Radiographics 2001;21 Spec No:237-254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11598260.

31. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3969475.

32. Janus CL, 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.

33. Seaman E, Goluboff ET, Ross S, Sawczuk IS. Association of radionuclide bone scan and serum alkaline phosphatase in patients with metastatic renal cell carcinoma. Urology 1996;48:692-695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8911510.

34. Shannon BA, Cohen RJ, de Bruto H, Davies RJ. The value of preoperative needle core biopsy for diagnosing benign lesions among small, incidentally detected renal masses. J Urol 2008;180:1257-1261; discussion 1261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18707712.

35. Park JW, Jo MK, Lee HM. Significance of 18F-fluorodeoxyglucose positron-emission tomography/computed tomography for the postoperative surveillance of advanced renal cell carcinoma. BJU Int 2009;103:615-619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19007371.

36. Amin MB, Edge SB, Greene F, et al., eds. AJCC Cancer Staging Manual, 8th ed. New York: Springer International Publishing; 2017.

37. Eble JN, Sauter G, Epstein JI, et al (eds). In: Pathology and genetics of tumours of the urinary systemand male genital organs. World Health Organization Classification of Tumours. Lyon: IARC Press, 2004.

38. Berger A, Brandina R, Atalla MA, et al. Laparoscopic radical nephrectomy for renal cell carcinoma: oncological outcomes at 10 years or more. J Urol 2009;182:2172-2176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19758651.

39. Burgess NA, Koo BC, Calvert RC, et al. Randomized trial of laparoscopic v open nephrectomy. J Endourol 2007;21:610-613. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17638555.

40. Chung SD, Huang KH, Lai MK, et al. Long-term follow-up of hand-assisted laparoscopic radical nephrectomy for organ-confined renal cell carcinoma. Urology 2007;69:652-655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17445645.

41. Gabr AH, Gdor Y, Strope SA, et al. Patient and pathologic correlates with perioperative and long-term outcomes of laparoscopic radical nephrectomy. Urology 2009;74:635-640. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19616826.

42. Hemal AK, Kumar A. A prospective comparison of laparoscopic and robotic radical nephrectomy for T1-2N0M0 renal cell carcinoma. World J Urol 2009;27:89-94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18704439.

43. Hemal AK, Kumar A, Kumar R, et al. Laparoscopic versus open radical nephrectomy for large renal tumors: a long-term prospective comparison. J Urol 2007;177:862-866. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17296361.

44. Luo JH, Zhou FJ, Xie D, et al. Analysis of long-term survival in patients with localized renal cell carcinoma: laparoscopic versus open radical nephrectomy. World J Urol 2010;28:289-293. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19916010.

45. Nambirajan T, Jeschke S, Al-Zahrani H, et al. Prospective, randomized controlled study: transperitoneal laparoscopic versus retroperitoneoscopic radical nephrectomy. Urology 2004;64:919-924. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15533478.

46. 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.

47. 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.

48. 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.

49. 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.

50. Zini L, Perrotte P, Capitanio U, et al. Radical versus partial nephrectomy: effect on overall and noncancer mortality. Cancer 2009;115:1465-1471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19195042.

51. Lee HJ, Liss MA, Derweesh IH. Outcomes of partial nephrectomy for clinical T1b and T2 renal tumors. Curr Opin Urol 2014;24:448-452. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24921904.

52. 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.

53. 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.

54. Thompson RH, Boorjian SA, Lohse CM, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. J Urol 2008;179:468-471; discussion 472-463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18076931.

55. 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.

56. 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.

57. Kim SP, Thompson RH, Boorjian SA, et al. Comparative effectiveness for survival and renal function of partial and radical nephrectomy for localized renal tumors: a systematic review and meta-analysis. J Urol 2012;188:51-57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22591957.

58. Thompson RH, Siddiqui S, Lohse CM, et al. Partial versus radical nephrectomy for 4 to 7 cm renal cortical tumors. J Urol 2009;182:2601-2606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19836797.

59. 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.

60. Shuch B, Lam JS, 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.

61. Chen DY, 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.

62. Tan HJ, Norton EC, Ye Z, et al. Long-term survival following partial vs radical nephrectomy among older patients with early-stage kidney cancer. JAMA 2012;307:1629-1635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22511691.

63. Gill IS, Kavoussi LR, Lane BR, et al. Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumors. J Urol 2007;178:41-46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17574056.

64. Gong EM, Orvieto MA, Zorn KC, et al. Comparison of laparoscopic and open partial nephrectomy in clinical T1a renal tumors. J Endourol 2008;22:953-957. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18363510.

65. Lane BR, Gill IS. 7-year oncological outcomes after laparoscopic and open partial nephrectomy. J Urol 2010;183:473-479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20006866.

66. 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.

67. 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.

68. 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.

69. Capitanio U, Becker F, Blute ML, et al. Lymph node dissection in renal cell carcinoma. Eur Urol 2011;60:1212-1220. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21940096.

70. 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.

71. Kuczyk M, Wegener G, 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.

72. O'Malley RL, Godoy G, Kanofsky JA, 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.

73. Lane BR, Tiong HY, Campbell SC, et al. Management of the adrenal gland during partial nephrectomy. J Urol 2009;181:2430-2436; discussion 2436-2437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19371896.

74. 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.

75. Abouassaly R, Lane BR, Novick AC. Active surveillance of renal masses in elderly patients. J Urol 2008;180:505-508; discussion 508-509. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18550113.

76. Lane BR, Abouassaly R, Gao T, et al. Active treatment of localized renal tumors may not impact overall survival in patients aged 75 years or older. Cancer 2010;116:3119-3126. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20564627.

77. Bird VG, Carey RI, Ayyathurai R, Bird VY. Management of renal masses with laparoscopic-guided radiofrequency ablation versus laparoscopic partial nephrectomy. J Endourol 2009;23:81-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19118475.

78. O'Malley RL, Berger AD, Kanofsky JA, et al. A matched-cohort comparison of laparoscopic cryoablation and laparoscopic partial nephrectomy for treating renal masses. BJU Int 2007;99:395-398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17092288.

79. Campbell S, Uzzo RG, Allaf ME, et al. Renal Mass and Localized Renal Cancer: AUA Guideline. J Urol 2017;198:520-529. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28479239.

80. Pierorazio PM, Johnson MH, Patel HD, et al. Management of Renal Masses and Localized Renal Cancer: Systematic Review and Meta-Analysis. J Urol 2016;196:989-999. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27157369.

81. Simmons MN, Weight CJ, Gill IS. Laparoscopic radical versus partial nephrectomy for tumors >4 cm: intermediate-term oncologic and functional

outcomes. Urology 2009;73:1077-1082. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19394509.

82. Peycelon M, Hupertan V, Comperat E, et al. Long-term outcomes after nephron sparing surgery for renal cell carcinoma larger than 4 cm. J Urol 2009;181:35-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19012929.

83. Smaldone MC, Fung C, Uzzo RG, Haas NB. Adjuvant and neoadjuvant therapies in high-risk renal cell carcinoma. Hematol Oncol Clin North Am 2011;25:765-791. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21763967.

84. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet 2016;387:2008-2016. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26969090.

85. Haas NB, Manola J, Dutcher JP, et al. Adjuvant Treatment for High-Risk Clear Cell Renal Cancer: Updated Results of a High-Risk Subset of the ASSURE Randomized Trial. JAMA Oncol 2017;3:1249-1252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28278333.

86. Motzer RJ, Haas NB, Donskov F, et al. Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma. J Clin Oncol 2017;35:3916-3923. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28902533.

87. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. N Engl J Med 2016;375:2246-2254. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27718781.

88. Motzer RJ, Ravaud A, Patard JJ, et al. Adjuvant Sunitinib for High-risk Renal Cell Carcinoma After Nephrectomy: Subgroup Analyses and Updated Overall Survival Results. Eur Urol 2018;73:62-68. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28967554.

89. Eggener SE, Yossepowitch O, Pettus JA, et al. Renal cell carcinoma recurrence after nephrectomy for localized disease: predicting survival from time of recurrence. J Clin Oncol 2006;24:3101-3106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16809736.

90. Stewart SB, Thompson RH, Psutka SP, et al. Evaluation of the National Comprehensive Cancer Network and American Urological Association renal cell carcinoma surveillance guidelines. J Clin Oncol 2014;32:4059-4065. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25403213.

91. Dabestani S, Beisland C, Stewart GD, et al. Long-term Outcomes of Follow-up for Initially Localised Clear Cell Renal Cell Carcinoma: RECUR Database Analysis. Eur Urol Focus 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29525381.

92. Mucksavage P, Kutikov A, Magerfleisch L, et al. Comparison of radiographical imaging modalities for measuring the diameter of renal masses: is there a sizeable difference? BJU Int 2011;108:E232-236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21348913.

93. Herr HW. Partial nephrectomy for incidental renal cell carcinoma. Br J Urol 1994;74:431-433. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7820418.

94. Morgan WR, Zincke H. Progression and survival after renal-conserving surgery for renal cell carcinoma: experience in 104 patients and extended followup. J Urol 1990;144:852-857. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2398558.

95. Adamy A, Chong KT, Chade D, et al. Clinical characteristics and outcomes of patients with recurrence 5 years after nephrectomy for localized renal cell carcinoma. J Urol 2011;185:433-438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21167521.

96. 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.

97. Culp SH, Tannir NM, Abel EJ, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? Cancer 2010;116:3378-3388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20564061.

98. Choueiri TK, Xie W, Kollmannsberger C, et al. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. J Urol 2011;185:60-66. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21074201.

99. Mejean A, Ravaud A, Thezenas S, et al. Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. N Engl J Med 2018;379:417-427. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29860937.

100. Motzer RJ, Russo P. Cytoreductive Nephrectomy - Patient Selection Is Key. N Engl J Med 2018;379:481-482. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29860908.

101. Siva S, Ellis RJ, Ponsky L, et al. Consensus statement from the International Radiosurgery Oncology Consortium for Kidney for primary renal cell carcinoma. Future Oncol 2016;12:637-645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26837701.

102. Siva S, Louie AV, Warner A, et al. Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). Cancer 2018;124:934-942. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29266183.

103. Meyer E, Pasquier D, Bernadou G, et al. Stereotactic radiation therapy in the strategy of treatment of metastatic renal cell carcinoma: A study of the Getug group. Eur J Cancer 2018;98:38-47. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29864737.

104. Eble J, Sauter G, Epstein J, et al. Pathology and genetics of tumours of the urinary system and male genital organs. In: World Health Organization Classification of Tumours. Lyon, France. IARC press; 2004:p. 7.

105. 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.

106. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009;27:5794-5799. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19826129.

107. Mekhail TM, Abou-Jawde RM, Boumerhi G, et al. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. J Clin Oncol 2005;23:832-841. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15681528.

108. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol 2013;14:141-148. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23312463.

109. 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.

110. Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer 2013;49:1287-1296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23321547.

111. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369:722-731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23964934.

112. Motzer RJ, Hutson TE, McCann L, et al. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. New England Journal of Medicine 2014;370:1769-1770. Available at: http://www.nejm.org/doi/full/10.1056/NEJMc1400731.

113. Escudier B, Porta C, Bono P, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. J Clin Oncol 2014;32:1412-1418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24687826.

114. 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.

115. 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.

116. Chow LQ, 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.

117. 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.

118. 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.

119. Gore ME, Szczylik C, Porta C, et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. Br J Cancer 2015;113:12-19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26086878.

120. Jonasch E, Slack RS, Geynisman DM, et al. Phase II Study of Two Weeks on, One Week off Sunitinib Scheduling in Patients With Metastatic Renal Cell Carcinoma. J Clin Oncol 2018;36:1588-1593. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29641297.

121. Ornstein MC, Wood LS, Elson P, et al. A Phase II Study of Intermittent Sunitinib in Previously Untreated Patients With Metastatic Renal Cell Carcinoma. J Clin Oncol 2017;35:1764-1769. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28113029.

122. Ruiz-Morales JM, Swierkowski M, Wells JC, et al. First-line sunitinib versus pazopanib in metastatic renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur J Cancer 2016;65:102-108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27487293.

123. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med 2018;378:1277-1290. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29562145.

124. Hammers HJ, Plimack ER, Infante JR, et al. Safety and Efficacy of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma: The CheckMate 016 Study. J Clin Oncol 2017;35:3851-3858. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28678668.

125. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. J Clin Oncol 2017;35:591-597. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28199818.

126. Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol

2016;17:1317-1324. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27498080.

127. Sonpavde G, Hutson TE, Rini BI. Axitinib for renal cell carcinoma. Expert Opin Investig Drugs 2008;17:741-748. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18447599.

128. Hutson TE, Lesovoy V, Al-Shukri S, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. Lancet Oncol 2013;14:1287-1294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24206640.

129. Rini BI, Melichar B, Ueda T, et al. Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomised double-blind phase 2 trial. Lancet Oncol 2013;14:1233-1242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24140184.

130. 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.

131. 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.

132. 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.

133. 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.

134. 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.

135. 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.

136. 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.

137. 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.

138. 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.

139. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1814-1823. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26406150.

140. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 2016;17:917-927. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27279544.

141. Motzer RJ, Escudier B, Powles T, et al. Long-term follow-up of overall survival for cabozantinib versus everolimus in advanced renal cell

carcinoma. Br J Cancer 2018;118:1176-1178. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29576624.

142. Cella D, Escudier B, Tannir NM, et al. Quality of Life Outcomes for Cabozantinib Versus Everolimus in Patients With Metastatic Renal Cell Carcinoma: METEOR Phase III Randomized Trial. J Clin Oncol 2018;36:757-764. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29377755.

143. Escudier B, Powles T, Motzer RJ, et al. Cabozantinib, a New Standard of Care for Patients With Advanced Renal Cell Carcinoma and Bone Metastases? Subgroup Analysis of the METEOR Trial. J Clin Oncol 2018:Jco2017747352. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29309249.

144. Amzal B, Fu S, Meng J, et al. Cabozantinib versus everolimus, nivolumab, axitinib, sorafenib and best supportive care: A network meta-analysis of progression-free survival and overall survival in second line treatment of advanced renal cell carcinoma. PLoS One 2017;12:e0184423. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28886175.

145. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1803-1813. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26406148.

146. Escudier B, Sharma P, McDermott DF, et al. CheckMate 025 Randomized Phase 3 Study: Outcomes by Key Baseline Factors and Prior Therapy for Nivolumab Versus Everolimus in Advanced Renal Cell Carcinoma. Eur Urol 2017;72:962-971. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28262413.

147. Cella D, Escudier B, Rini B, et al. Patient-reported outcomes for axitinib vs sorafenib in metastatic renal cell carcinoma: phase III (AXIS) trial. Br J Cancer 2013;108:1571-1578. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23579211.

148. Escudier B, Motzer RJ, Sharma P, et al. Treatment Beyond Progression in Patients with Advanced Renal Cell Carcinoma Treated with Nivolumab in CheckMate 025. Eur Urol 2017;72:368-376. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28410865.

149. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011;378:1931-1939. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22056247.

150. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol 2013;14:552-562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23598172.

151. Rini BI, de La Motte Rouge T, Harzstark AL, et al. Five-year survival in patients with cytokine-refractory metastatic renal cell carcinoma treated with axitinib. Clin Genitourin Cancer 2013;11:107-114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23391371.

152. Escudier B, Michaelson MD, Motzer RJ, et al. Axitinib versus sorafenib in advanced renal cell carcinoma: subanalyses by prior therapy from a randomised phase III trial. Br J Cancer 2014;110:2821-2828. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24823696.

153. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol 2015;16:1473-1482. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26482279.

154. Motzer RJ, Hutson TE, Ren M, et al. Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. Lancet Oncol 2016;17:e4-5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26758760.

155. 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.

156. 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.

157. Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. J Clin Oncol 2014;32:2765-2772. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25049330.

158. Knox JJ, Barrios CH, Kim TM, et al. Final overall survival analysis for the phase II RECORD-3 study of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic RCC. Ann Oncol 2017;28:1339-1345. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28327953.

159. Hainsworth JD, Rubin MS, Arrowsmith ER, et al. Pazopanib as second-line treatment after sunitinib or bevacizumab in patients with advanced renal cell carcinoma: a Sarah Cannon Oncology Research Consortium Phase II Trial. Clin Genitourin Cancer 2013;11:270-275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23665131.

160. Matrana MR, Duran C, Shetty A, et al. Outcomes of patients with metastatic clear-cell renal cell carcinoma treated with pazopanib after disease progression with other targeted therapies. Eur J Cancer 2013;49:3169-3175. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23810246.

161. 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.

162. 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.

163. 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.

164. 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.

165. 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.

166. Garcia JA, Hutson TE, Elson P, et al. Sorafenib in patients with metastatic renal cell carcinoma refractory to either sunitinib or bevacizumab. Cancer 2010;116:5383-5390. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20806321.

167. 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.

168. 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.

169. 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.

170. 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.

171. 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.

172. 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.

173. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009;27:3312-3318. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19451442.

174. Di Lorenzo G, Carteni G, Autorino R, et al. Phase II study of sorafenib in patients with sunitinib-refractory metastatic renal cell cancer. J Clin Oncol 2009;27:4469-4474. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19652053.

175. 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.

176. Sheng X, Chi Z, Cui C, et al. Efficacy and safety of sorafenib versus sunitinib as first-line treatment in patients with metastatic renal cell carcinoma: largest single-center retrospective analysis. Oncotarget 2016;7:27044-27054. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26894858.

177. Cai W, Kong W, Dong B, et al. Comparison of efficacy, safety, and quality of life between sorafenib and sunitinib as first-line therapy for Chinese patients with metastatic renal cell carcinoma. Chin J Cancer 2017;36:64. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28789709.

178. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 2003;349:427-434. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12890841.

179. Atkins MB, Hidalgo M, Stadler WM, et al. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. J Clin Oncol 2004;22:909-918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14990647.

180. Hutson TE, Escudier B, Esteban E, et al. Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol 2014;32:760-767. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24297950.

181. Hwang C, Heath EI. The Judgment of Paris: treatment dilemmas in advanced renal cell carcinoma. J Clin Oncol 2014;32:729-734. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24516012.

182. de Velasco G, McKay RR, Lin X, et al. Comprehensive Analysis of Survival Outcomes in Non-Clear Cell Renal Cell Carcinoma Patients Treated in Clinical Trials. Clin Genitourin Cancer 2017;15:652-660 e651. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28410911.

183. 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.

184. Choueiri TK, Plantade A, Elson P, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. J Clin Oncol 2008;26:127-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18165647.

185. Tannir NM, Plimack E, Ng C, et al. A phase 2 trial of sunitinib in patients with advanced non-clear cell renal cell carcinoma. Eur Urol 2012;62:1013-1019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22771265.

186. Lee JL, Ahn JH, Lim HY, et al. Multicenter phase II study of sunitinib in patients with non-clear cell renal cell carcinoma. Ann Oncol 2012;23:2108-2114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22228449.

187. Molina AM, Feldman DR, Ginsberg MS, et al. Phase II trial of sunitinib in patients with metastatic non-clear cell renal cell carcinoma. Invest New Drugs 2012;30:335-340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20711632.

188. Shi HZ, Tian J, Li CL. Safety and efficacy of sunitinib for advanced non-clear cell renal cell carcinoma. Asia Pac J Clin Oncol 2015;11:328-333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26471774.

189. Ravaud A, Oudard S, De Fromont M, et al. First-line treatment with sunitinib for type 1 and type 2 locally advanced or metastatic papillary renal cell carcinoma: a phase II study (SUPAP) by the French Genitourinary Group (GETUG)dagger. Ann Oncol 2015;26:1123-1128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25802238.

190. Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. Lancet Oncol 2016;17:378-388. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26794930.

191. Tannir NM, Jonasch E, Albiges L, et al. Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (ESPN): a randomized multicenter phase 2 trial. Eur Urol 2016;69:866-874. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26626617.

192. Ciccarese C, Iacovelli R, Brunelli M, et al. Addressing the best treatment for non-clear cell renal cell carcinoma: A meta-analysis of randomised clinical trials comparing VEGFR-TKis versus mTORi-targeted therapies. Eur J Cancer 2017;83:237-246. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28756136.

193. Campbell MT, Bilen MA, Shah AY, et al. Cabozantinib for the treatment of patients with metastatic non-clear cell renal cell carcinoma: A retrospective analysis. Eur J Cancer 2018;104:188-194. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30380460.

194. Martinez Chanza N, Bossé D, Bilen MA, et al. Cabozantinib (Cabo) in advanced non-clear cell renal cell carcinoma (nccRCC): A retrospective multicenter analysis. Journal of Clinical Oncology 2018;36:4579-4579. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.4579.

195. Prisciandaro M, Ratta R, Massari F, et al. Safety and Efficacy of Cabozantinib for Metastatic Nonclear Renal Cell Carcinoma: Real-world Data From an Italian Managed Access Program. Am J Clin Oncol 2019;42:42-45. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30204614.

196. Blank CU, Bono P, Larkin JMG, et al. Safety and efficacy of everolimus in patients with non-clear cell renal cell carcinoma refractory to VEGF-targeted therapy: Subgroup analysis of REACT [abstract]. J Clin Oncol 2012;30 (5_suppl):Abstract 402. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2012.30.5_suppl.402.

197. Larkin JM, Fisher RA, Pickering LM, et al. Chromophobe renal cell carcinoma with prolonged response to sequential sunitinib and everolimus. J Clin Oncol 2011;29:e241-242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21245426.

198. Koh Y, Lim HY, Ahn JH, et al. Phase II trial of everolimus for the treatment of nonclear-cell renal cell carcinoma. Ann Oncol 2013;24:1026-1031. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23180114.

199. Escudier B, Molinie V, Bracarda S, et al. Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis. Eur J Cancer 2016;69:226-235. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27680407.

200. A phase II efficacy trial of pazopanib in non-clear cell metastatic renal cell cancer (mRCC) PINCR (Clinical Trial ID: NCT01767636. Available at: https://clinicaltrials.gov/ct2/show/NCT01767636.

201. Jung KS, Lee SJ, Park SH, et al. Pazopanib for the Treatment of Non-clear Cell Renal Cell Carcinoma: A Single-Arm, Open-Label, Multicenter, Phase II Study. Cancer Res Treat 2018;50:488-494. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28546525.

202. Park I, Lee SH, Lee JL. A Multicenter Phase II Trial of Axitinib in Patients With Recurrent or Metastatic Non-clear-cell Renal Cell Carcinoma Who Had Failed Prior Treatment With Temsirolimus. Clin Genitourin Cancer 2018;16:e997-e1002. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29903415.

203. Buti S, Bersanelli M, Maines F, et al. First-Line PAzopanib in NOn-clear-cell Renal cArcinoMA: The Italian Retrospective Multicenter PANORAMA Study. Clin Genitourin Cancer 2017;15:e609-e614. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28108284.

204. Irshad T, Olencki T, Zynger DL, et al. Bevacizumab in metastatic papillary renal cell carcinoma (PRCC). ASCO Meeting Abstracts 2011;29:e15158. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2011.29.15_suppl.e15158.

205. 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

206. Koshkin VS, Barata PC, Zhang T, et al. Clinical activity of nivolumab in patients with non-clear cell renal cell carcinoma. J Immunother Cancer 2018;6:9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29378660.

207. McKay RR, Bosse D, Xie W, et al. The Clinical Activity of PD-1/PD-L1 Inhibitors in Metastatic Non-Clear Cell Renal Cell Carcinoma. Cancer Immunol Res 2018;6:758-765. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29748390.

208. Menko FH, Maher ER, Schmidt LS, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. Fam Cancer 2014;13:637-644. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25012257.

209. Srinivasan R, Su D, Stamatakis L, et al. Mechanism based targeted therapy for hereditary leiomyomatosis and renal cell cancer (HLRCC) and sporadic papillary renal cell carcinoma: interim results from a phase 2 study of bevacizumab and erlotinib [abstract]. Eur J Cancer 2014;50:8. Available at: http://www.ejcancer.com/article/S0959-8049(14)70131-5/abstract.

210. Voss MH, Molina AM, Chen YB, et al. Phase II Trial and Correlative Genomic Analysis of Everolimus Plus Bevacizumab in Advanced Non-Clear Cell Renal Cell Carcinoma. J Clin Oncol 2016;34:3846-3853. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27601542.

211. 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.

212. Venugopal B, Ansari J, Aitchison M, et al. Efficacy of temsirolimus in metastatic chromophobe renal cell carcinoma. BMC Urol 2013;13:26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23688003.

213. Chowdhury S, Matrana MR, Tsang C, et al. Systemic therapy for metastatic non-clear-cell renal cell carcinoma: recent progress and future directions. Hematol Oncol Clin North Am 2011;25:853-869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21763971.

214. Patard JJ, Leray E, Rioux-Leclercq N, et al. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. J Clin Oncol 2005;23:2763-2771. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15837991.

215. Cheville JC, Lohse CM, Zincke H, et al. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Am

J Surg Pathol 2003;27:612-624. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12717246.

216. Cheville JC, Lohse CM, Zincke H, et al. Sarcomatoid renal cell carcinoma: an examination of underlying histologic subtype and an analysis of associations with patient outcome. Am J Surg Pathol 2004;28:435-441. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15087662.

217. Shuch B, Bratslavsky G, Linehan WM, Srinivasan R. Sarcomatoid Renal Cell Carcinoma: A Comprehensive Review of the Biology and Current Treatment Strategies. The Oncologist 2012;17:46-54. Available at: http://theoncologist.alphamedpress.org/content/17/1/46.abstract.

218. Keskin SK, Msaouel P, Hess KR, et al. Outcomes of Patients with Renal Cell Carcinoma and Sarcomatoid Dedifferentiation Treated with Nephrectomy and Systemic Therapies: Comparison between the Cytokine and Targeted Therapy Eras. J Urol 2017;198:530-537. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28411072.

219. 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.

220. Dutcher JP, Nanus D. Long-term survival of patients with sarcomatoid renal cell cancer treated with chemotherapy. Med Oncol 2011;28:1530-1533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20717755.

221. Haas NB, Lin X, Manola J, et al. A phase II trial of doxorubicin and gemcitabine in renal cell carcinoma with sarcomatoid features: ECOG 8802. Med Oncol 2012;29:761-767. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21298497.

222. Richey SL, Ng C, Lim ZD, et al. Durable remission of metastatic renal cell carcinoma with gemcitabine and capecitabine after failure of targeted therapy. J Clin Oncol 2011;29:e203-205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21172884.

223. Tannir NM, Thall PF, Ng CS, et al. A phase II trial of gemcitabine plus capecitabine for metastatic renal cell cancer previously treated with immunotherapy and targeted agents. J Urol 2008;180:867-872; discussion 872. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18635226.

224. Stadler WM, Halabi S, Rini B, et al. A phase II study of gemcitabine and capecitabine in metastatic renal cancer: a report of Cancer and Leukemia Group B protocol 90008. Cancer 2006;107:1273-1279. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16909426.

225. Michaelson MD, McKay RR, Werner L, et al. Phase 2 trial of sunitinib and gemcitabine in patients with sarcomatoid and/or poor-risk metastatic renal cell carcinoma. Cancer 2015;121:3435-3443. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26058385.

226. Maiti A, Nemati-Shafaee M, Msaouel P, et al. Phase 2 Trial of Capecitabine, Gemcitabine, and Bevacizumab in Sarcomatoid Renal-Cell Carcinoma. Clin Genitourin Cancer 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28870517.

227. A randomized phase II trial of sunitinib/gemcitabine or sunitinib in advanced renal cell carcinoma with sarcomatoid features (Clinical Trial ID: NCT01164228). Available at: https://clinicaltrials.gov/ct2/show/NCT01164228.

228. Hakimi AA, Koi PT, Milhoua PM, et al. Renal medullary carcinoma: the Bronx experience. Urology 2007;70:878-882. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18068443.

229. Watanabe IC, Billis A, Guimaraes MS, et al. Renal medullary carcinoma: report of seven cases from Brazil. Mod Pathol 2007;20:914-920. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17643096.

230. Shah AY, Karam JA, Malouf GG, et al. Management and outcomes of patients with renal medullary carcinoma: a multicentre collaborative study. BJU Int 2017;120:782-792. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27860149.

231. Srigley JR, Delahunt B. Uncommon and recently described renal carcinomas. Mod Pathol 2009;22 Suppl 2:S2-S23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19494850.

232. Tokuda N, Naito S, Matsuzaki O, et al. Collecting duct (Bellini duct) renal cell carcinoma: a nationwide survey in Japan. J Urol 2006;176:40-43; discussion 43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16753362.

233. Karakiewicz PI, Trinh QD, Rioux-Leclercq N, et al. Collecting duct renal cell carcinoma: a matched analysis of 41 cases. Eur Urol 2007;52:1140-1145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17336449.

234. Gupta R, Billis A, Shah RB, et al. Carcinoma of the collecting ducts of Bellini and renal medullary carcinoma: clinicopathologic analysis of 52 cases of rare aggressive subtypes of renal cell carcinoma with a focus on their interrelationship. Am J Surg Pathol 2012;36:1265-1278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22895263.

235. Oudard S, Banu E, Vieillefond A, et al. Prospective multicenter phase II study of gemcitabine plus platinum salt for metastatic collecting duct carcinoma: results of a GETUG (Groupe d'Etudes des Tumeurs Uro-Genitales) study. J Urol 2007;177:1698-1702. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17437788.

236. Stadler WM, Figlin RA, McDermott DF, et al. Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. Cancer 2010;116:1272-1280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20082451.

237. Beck J, Procopio G, Bajetta E, et al. Final results of the European Advanced Renal Cell Carcinoma Sorafenib (EU-ARCCS) expanded-access study: a large open-label study in diverse community settings. Ann Oncol 2011;22:1812-1823. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21324953.

238. Fokas E, Henzel M, Hamm K, et al. Radiotherapy for brain metastases from renal cell cancer: should whole-brain radiotherapy be added to stereotactic radiosurgery?: analysis of 88 patients. Strahlenther Onkol 2010;186:210-217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20165820.

239. Zekri J, Ahmed N, Coleman RE, Hancock BW. The skeletal metastatic complications of renal cell carcinoma. Int J Oncol 2001;19:379-382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11445855.

240. Schlesinger-Raab A, Treiber U, Zaak D, et al. Metastatic renal cell carcinoma: results of a population-based study with 25 years follow-up. Eur J Cancer 2008;44:2485-2495. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18783939.

241. Roza T, Hakim L, van Poppel H, Joniau S. Bone-targeted therapies for elderly patients with renal cell carcinoma: current and future directions. Drugs Aging 2013;30:877-886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24072355.

242. Hunter GK, Balagamwala EH, Koyfman SA, et al. The efficacy of external beam radiotherapy and stereotactic body radiotherapy for painful spinal metastases from renal cell carcinoma. Pract Radiat Oncol 2012;2:e95-e100. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24674192.

243. Zelefsky MJ, Greco C, Motzer R, et al. Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. Int J Radiat Oncol Biol Phys 2012;82:1744-1748. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21596489.

244. Lipton A, Zheng M, 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.

245. Rosen LS, Gordon D, Tchekmedyian 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.

246. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 2011;29:1125-1132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21343556.