HHS Public Access

Author manuscript

J Natl Compr Canc Netw. Author manuscript; available in PMC 2023 May 17.

Published in final edited form as:

J Natl Compr Canc Netw. 2020 September ; 18(9): 1160–1170. doi:10.6004/jnccn.2020.0043.

Kidney Cancer, Version 1.2021:

Featured Updates to the NCCN Guidelines

Robert J. Motzer, MD[1], **Eric Jonasch, MD**[2], **Shawna Boyle, MD**[3], **Maria I. Carlo, MD**[1], **Brandon Manley, MD**[4], **Neeraj Agarwal, MD**[5], **Ajjai Alva, MBBS**[6], **Katy Beckermann, MD, PhD**[7], **Toni K. Choueiri, MD**[8], **Brian A. Costello, MD, MS**[9], **Ithaar H. Derweesh, MD**[10], **Arpita Desai, MD**[11], **Saby George, MD**[12], **John L. Gore, MD, MS**[13], **Naomi Haas, MD**[14], **Steven L. Hancock, MD**[15], **Christos Kyriakopoulos, MD**[16], **Elaine T. Lam, MD**[17], **Clayton Lau, MD**[18], **Bryan Lewis**[19], **David C. Madoff, MD**[20], **Brittany McCreery, MD, MBA**[13], **M. Dror Michaelson, MD, PhD**[21], **Amir Mortazavi, MD**[22], **Lakshminarayanan Nandagopal, MD**[23], **Phillip M. Pierorazio, MD**[24], **Elizabeth R. Plimack, MD, MS**[25], **Lee Ponsky, MD**[26], **Sundhar Ramalingam, MD**[27], **Brian Shuch, MD**[28], **Zachary L. Smith, MD**[29], **Bradley Somer, MD**[30], **Jeffrey Sosman, MD**[31], **Mary A. Dwyer, MS, CGC**[32], **Angela D. Motter, PhD**[32]

[1]Memorial Sloan Kettering Cancer Center

[2]The University of Texas MD Anderson Cancer Center

[3]Fred & Pamela Buffett Cancer Center

[4]Moffitt Cancer Center

[5]Huntsman Cancer Institute at the University of Utah

[6]University of Michigan Rogel Cancer Center

[7]Vanderbilt-Ingram Cancer Center

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their application or use in any way.

The complete and most recent version of these NCCN Guidelines is available free of charge at NCCN.org.

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

Kerrin M. Rosenthal, MA; Kimberly Callan, MS; Genevieve Emberger Hartzman, MA; Erin Hesler; Kristina M. Gregory, RN, MSN, OCN; Rashmi Kumar, PhD; Karen Kanefield; and Kathy Smith.

Individuals Who Provided Content Development and/or Authorship Assistance:

Robert J. Motzer, MD, Panel Chair, has disclosed that he has received grant/research support and consulting fees from Pfizer, Exelixis, Eisai, Genentech, Roche, and Novartis.

Eric Jonasch, MD, Panel Vice Chair, has disclosed that he receives grant/research support from Pfizer, Exelixis, Novartis, and Merck, and that he receives honoraria from Pfizer, Exelixis, Eisai, Ipsen, Novartis, Merck, Roche, and Genentech.

Shawna Boyle, MD, Panel Member, has disclosed that she has no relevant financial relationships.

Maria I. Carlo, MD, Panel Member, has disclosed that she has no relevant financial disclosures.

Brandon Manley, MD, Panel Member, has disclosed that he has no relevant financial relationships.

Angela D. Motter, PhD, Oncology Scientist/Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

[8]Dana-Farber/Brigham and Women's Cancer Center

[9]Mayo Clinic Cancer Center

[10]UC San Diego Moores Cancer Center

[11]UCSF Helen Diller Family Comprehensive Cancer Center

[12]Roswell Park Comprehensive Cancer Center

[13]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

[14]Abramson Cancer Center at the University of Pennsylvania

[15]Stanford Cancer Institute

[16]University of Wisconsin Carbone Cancer Center

[17]University of Colorado Cancer Center

[18]City of Hope National Medical Center

[19]Kidney Cancer Coalition

[20]Yale Cancer Center/Smilow Cancer Hospital

[21]Massachusetts General Hospital Cancer Center

[22]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

[23]O'Neal Comprehensive Cancer Center at UAB

[24]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

[25]Fox Chase Cancer Center

[26]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

[27]Duke Cancer Institute

[28]UCLA Jonsson Comprehensive Cancer Center

[29]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

[30]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center

[31]Robert H. Lurie Comprehensive Cancer Center of Northwestern University

[32]National Comprehensive Cancer Network.

Abstract

The NCCN Guidelines for Kidney Cancer provide multidisciplinary recommendations for diagnostic workup, staging, and treatment of patients with renal cell carcinoma (RCC). These NCCN Guidelines Insights focus on recent updates to the guidelines, including changes to certain systemic therapy recommendations for patients with relapsed or stage IV RCC. They also discuss

the addition of a new section to the guidelines that identifies and describes the most common hereditary RCC syndromes and provides recommendations for genetic testing, surveillance, and/or treatment options for patients who are suspected or confirmed to have one of these syndromes.

Overview

An estimated 73,800 new cases of cancers of the kidney and renal pelvis will be diagnosed in the United States in 2020, and 14,800 people will die of the disease.[1] Approximately 85% of all kidney tumors are renal cell carcinoma (RCC), and approximately 70% of RCC cases are of clear cell histology (ccRCC).[2–4] Approximately 3% of RCC cases are hereditary, although some hereditary RCC may present without a known family history. Multiple familial RCC syndromes that may confer increased risk of developing RCC have been identified, as have their causative genetic mutations.[5,6]

Histologic diagnosis of RCC is typically established after surgical removal of renal tumors or after biopsy. Tumor histology, disease stage, and risk stratification of patients is important in therapy selection. Analysis of the SEER database indicates that RCC incidence has been stable and death rates have been declining on average 0.9% each year from 2007 through 2016.[7] Approximately 75% of people with kidney cancer survive ≥5 years after diagnosis. Prognosis varies widely according to stage at diagnosis. Patients initially diagnosed with clinically localized RCC that is confined to the primary site have a higher 5-year survival (92.5%), largely as a result of surgical interventions, compared with patients initially diagnosed with distant cancer that has metastasized, among which only 12% survive 5 years.[7]

Regardless of tumor histology, treatment of patients with nonmetastatic primary RCC typically consists of surgery (ie, nephrectomy). Systemic therapy options for patients with relapsed or stage IV disease include kinase inhibitors, mTOR inhibitors, and monoclonal antibodies against VEGF, PD-1, or PD-L1. Recommended systemic therapy regimens vary by patient risk status and tumor histology.

These NCCN Guidelines Insights focus on recent changes to systemic therapy recommendations for relapsed or stage IV RCC with clear cell or nonclear cell histology. Combination axitinib/pembrolizumab was added to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Kidney Cancer in version 4.2019 for treating relapsed or stage IV ccRCC in a second-line or higher setting (see KID-C page 1 of 2, above), whereas combination lenvatinib/everolimus was restratified in version 1.2021 according to the NCCN Categories of Preference for treating relapsed or stage IV nonclear cell RCC (nccRCC; see KID-C page 2 of 2, page 1163). This article also discusses are newly added information about 7 of the most common hereditary RCC syndromes, as well as genetic risk assessment, testing, surveillance, and treatment recommendations for patients who are suspected or confirmed to have one of these syndromes (see HRCC-1, HRCC-2, GENE-1, HRCC-B page 1 of 2, HRCC-C page 1 of 2, and HRCC-D, pages 1164–1169, respectively).

NCCN Categories of Preference

Starting with version 1.2019, the panel assigned a Category of Preference to all systemic therapy regimens included in the NCCN Guidelines for Kidney Cancer. The 3 NCCN Categories of Preference are as follows:

- Preferred: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability
- Other recommended: 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)

The Categories of Preference provide increased granularity and specificity of recommended regimens, and supplement information provided by the NCCN Categories of Evidence and Consensus (ie, categories 1, 2A, 2B, and 3).

Systemic Therapy Regimens for Relapsed or Stage IV Disease

Combination Axitinib/Pembrolizumab for ccRCC in a Second-Line or Higher Setting

In April 2019, the FDA approved pembrolizumab in combination with axitinib for first-line treatment of patients with advanced RCC.[8,9] Data from the KEYNOTE-426 trial, which included 861 patients, supported the combination therapy's approval for this indication.[10] In an interim version 4.2019 guidelines update, the panel added axitinib/pembrolizumab as a preferred first-line therapy option for patients in both the favorable and poor/intermediate International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups. For the same update, the panel also discussed whether axitinib/pembrolizumab might be used in clinical practice as an off-label second-line treatment option in patients with relapsed or stage IV ccRCC. Although the panel conceded that there were no published data to support the use of axitinib/pembrolizumab in a second-line setting, they thought that clinicians were likely to consider the combination therapy as a treatment option in patients with advanced ccRCC whose disease progressed after first-line sunitinib therapy. Thus, they unanimously agreed to add axitinib/pembrolizumab as an "other recommended" option for second-line or higher treatment of relapsed or stage IV ccRCC (see KID-C page 1 of 2, page 1162). The panel gave the combination therapy a category 2A rating because there were no published data to support this recommendation, but noted that they would need to revisit the rating if data on axitinib/pembrolizumab's use in a second-line or higher setting became available.

Combination Lenvatinib/Everolimus for Relapsed or Stage IV nccRCC

In May 2016, the FDA approved lenvatinib, a multitarget kinase inhibitor, in combination with everolimus, an mTOR inhibitor, for treating advanced RCC following one prior antiangiogenic therapy.[11,12] Data from a randomized phase II trial[13] partially supported the combination therapy's approval for this indication. The trial enrolled patients with advanced

or metastatic ccRCC whose disease had progressed after treatment with a VEGF-targeted therapy. Based on these data, in version 3.2016, the panel added lenvatinib/everolimus as a category 2A recommendation for treating relapsed or stage IV ccRCC in a second-line or higher setting.

For patients with relapsed or stage IV nccRCC, the benefit of targeted therapy is generally less clear.[14] Although the panel recommends enrollment in a clinical trial as a preferred option for these patients, they have established that certain systemic therapy options recommended for patients with ccRCC may also have some efficacy in those with nccRCC, even in the absence of clinical trial data. Despite the fact that the aforementioned lenvatinib/everolimus trial[13] only enrolled patients with ccRCC, the panel discussed whether the combination therapy might also be appropriate for use in patients with nccRCC. In version 1.2017, they added lenvatinib/everolimus as a category 2A recommendation for patients with relapsed or stage IV nccRCC. In version 1.2019, when Categories of Preference were added to the NCCN Guidelines for Kidney Cancer, the panel categorized lenvatinib/everolimus as "useful under certain circumstances" systemic therapy regimen for patients with relapsed or stage IV nccRCC; its category 2A recommendation did not change.

When considering updates to version 1.2021 of the guidelines, the panel reviewed newly available conference abstract data[15] from an ongoing single-arm phase II trial (ie, ClinicalTrials.gov identifier: NCT02915783) enrolling 31 patients with unresectable advanced or metastatic nccRCC who had not previously received chemotherapy. All patients in the trial received combination lenvatinib/everolimus. The investigators reported an objective response rate (ORR) of 25.8% (95% CI, 11.9%–44.6%); 8 patients in the trial achieved a partial response (PR; papillary, n53; chromophobe, n54; unclassified, n51) and none had a complete response (CR). At the time of data reporting, the median duration of response was not reached. A total of 18 patients (58.1%) had stable disease (SD), and the clinical benefit rate (CR + PR 1 durable SD [duration ≥23 weeks]) was 61.3% (95% CI, 42.2%–78.2%). Median progression-free survival was 9.23 months (95% CI, 5.49–not estimable [NE]) and median overall survival was 15.64 months (95% CI, 9.23–NE).

Although the panel conceded that these data had not yet been published and that the number of enrolled patients was small, they generally felt that lenvatinib/everolimus treatment led to improved patient outcomes across all nccRCC subtypes. Thus, the overwhelming majority agreed to reclassify lenvatinib/everolimus as an "other recommended" systemic therapy regimen for patients with nccRCC; the Category of Evidence and Consensus rating remained as 2A (see KID-C page 2 of 2, page 1163).

Hereditary RCC Syndromes: Clinical Features, Genetic Testing, and Surveillance

Although hereditary RCC is relatively rare (~3% of all cases),[5] the panel felt that it was important to provide recommendations for patients with a suspected or confirmed hereditary RCC syndrome, and thus established a subcommittee of panel members to develop a new section on hereditary RCC. Accordingly, version 1.2021 of the NCCN Guidelines for Kidney Cancer describes 7 of the most common hereditary RCC syndromes that may predispose patients to RCC: *BAP1* tumor predisposition syndrome (*BAP1*-TPDS), BirtHogg-Dubé syndrome (BHDS), hereditary leiomyomatosis and renal cell

cancer (HLRCC), hereditary papillary renal carcinoma (HPRC), hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC), tuberous sclerosis (TSC), and Von Hippel-Lindau (VHL) disease. The guidelines describe kidney-specific clinical features and manifestations of each of these syndromes and known associated genes/inheritance patterns, and provide genetic testing, surveillance, and treatment recommendations for patients who are suspected or confirmed to have a hereditary RCC syndrome. Although published data informed most of these recommendations, the panel also relied on the real-world experience and expertise of the hereditary subcommittee to develop recommendations in instances of limited data.

While discussing the potential scope and content of this new section, the subcommittee noted that there are some syndromes associated with RCC that overlap with other cancers (eg, Cowden syndrome, Lynch syndrome). For Cowden and Lynch syndromes, the panel refers readers to the information provided in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and Genetic/Familial High-Risk Assessment: Colorectal, respectively (available at NCCN.org). Future versions of the guidelines may be expanded to include other hereditary syndromes, such as microphthalmia-associated transcription factor (MiTF)–related cancer syndrome, which predisposes patients to melanoma and/or RCC.[6]

The subcommittee also noted that patients with hereditary RCC syndromes often experience nonrenal manifestations, but they felt that input from clinicians from other specialties (eg, dermatology, endocrinology, neurology, ophthalmology, urology) would be necessary to provide consensus-based recommendations for all potential manifestations. Accordingly, they limited the scope of this new section in version 1.2021 to only include kidney-specific clinical features and manifestations, but identified specialists who may be helpful in managing nonrenal manifestations in patients with a hereditary RCC syndrome (see HRCC-2, page 1165).

Recommendations for genetic testing, surveillance, and treatment vary according to the patient's personal and/or family history of a hereditary RCC syndrome or clinical diagnosis of RCC. Following is a summary of recommendations by patient population and the panel's rationale for these recommendations.

Recommendations for Patients With a Personal or Family History of an RCC Syndrome

The panel recommends that patients with a personal or family history of an RCC syndrome who have not yet been diagnosed with RCC should undergo genetic evaluation (see HRCC-1, page 1164). If patients harbor a pathogenic or likely pathogenic genetic mutation associated with an RCC syndrome, they should undergo screening for the development of RCC.

For screening in patients who are confirmed to have a hereditary RCC syndrome, the panel recommends use of MRI (preferred). CT may also be used for surgical planning purposes, but the panel warns that use of abdominal CT should be limited due to the potential of increased lifetime radiation exposure. The panel also includes recommendations on testing intervals and the age at which patients should begin regular screening, because both vary

widely by the hereditary RCC syndrome in question. Although patients with HLRCC should undergo imaging annually,[16] those with less aggressive syndromes such as PGL/PCC may benefit from testing at longer intervals.[17–19] For a detailed list of these recommendations, see HRCC-B page 1 of 2 (above).

The age at which patients should begin screening also varies by hereditary RCC syndrome (see HRCC-B page 1 of 2, above). Thus, the panel recommends that patients with confirmed HLRCC, PGL/PCC, TSC, and VHL disease begin screening in childhood.[16–20] In contrast, those with *BAP1*-TPDS, BHDS, or HPRC should begin screening in adulthood (ie, age 20 years for BHDS, age 30 years for *BAP1*-TPDS and HPRC).[17,21–23] However, the panel notes that if a patient has a known family member with an early diagnosis of hereditary RCC, screening should begin 10 years before the age that the family member was diagnosed, regardless of the syndrome in question.

Recommendations for Patients With RCC Who Have Characteristics Consistent With Inherited RCC

Although most of the new hereditary RCC section in version 1.2021 of the guidelines focuses on patients who have not yet been clinically diagnosed with RCC, the panel felt that they should also include recommendations for patients who already have a clinical or pathologic diagnosis of RCC and have characteristics potentially associated with a hereditary syndrome (eg, RCC diagnosis at ≤46 years of age, presence of bilateral or multifocal tumors, and/or ≥1 known first- or second-degree relative with RCC). These patients should also undergo genetic risk assessment and, if indicated, genetic testing. If inherited RCC is confirmed, patients should undergo screening as described earlier, in addition to disease stage-appropriate surveillance (see GENE-1, page 1166).

Surgical Recommendations for Patients With a Confirmed Hereditary RCC Syndrome

The panel also provides surgical recommendations for most of the included hereditary RCC syndromes (see HRCC-C page 1 of 2, above), which are based on published data and/or the subcommittee's real-world experience in treating patients with these syndromes. To develop these recommendations, they carefully weighed the potential morbidity and mortality of surgical treatment against the potential aggressiveness of each of the syndromes. They agreed that patients with BHDS, HPRC, and TSC may benefit from more conservative treatment, such as nephron-sparing surgery or ablative therapies,[24,25] whereas patients with HLRCC should undergo total radical nephrectomy.[16] The panel's recommendations for surgical treatment of PGL/PCC vary by tumor size and histology: those with smaller, less-aggressive tumors may be eligible for partial nephrectomy, whereas those with larger, more-aggressive tumors (eg, high-grade, sarcomatoid) should undergo radical nephrectomy.[26] Tumor size also factored into the panel's surgical recommendations for patients with VHL disease; they noted that these patients are likely to undergo multiple surgical resections during their lifetime that may contribute to chronic and progressive renal failure. Thus, the timing of surgical intervention must be carefully determined to limit both the development of metastases and morbidity associated with surgical intervention. They agreed that only patients with VHL disease with tumors approaching 3 cm in diameter should undergo partial nephrectomy (or ablative therapy if nephrectomy is contraindicated).[25,27]

Systemic Therapy for Patients With a Confirmed Hereditary RCC Syndrome

Version 1.2021 of the guidelines includes a limited number of kidney-specific systemic therapy options for patients with hereditary RCC (see HRCC-D, page 1169). While discussing potential content for this new section, the panel noted a lack of FDA-approved systemic therapy regimens for most of the included hereditary RCC syndromes. Among the included hereditary RCC syndromes, only TSC has an FDA-approved systemic therapy regimen: the mTOR inhibitor everolimus was approved in April 2012 for treating TSC-associated benign renal angiomyolipomas not requiring immediate surgery.[28,29]

The panel also included erlotinib/bevacizumab for patients with HLRCC-associated metastatic RCC and pazopanib for those with VHL disease–associated nonmetastatic lesions. Although these systemic therapy regimens are not FDA-approved for use in these patient populations, their inclusion is supported by clinical trial data showing improved patient outcomes. Erlotinib/bevacizumab treatment led to a 60% ORR and a median progression-free survival of 24.2 months in 20 patients with HLRCC-associated RCC,[30] whereas pazopanib led to a 42% ORR and a 52% renal tumor–specific response rate in 31 patients with VHL disease.[31] It is important to note that the panel's inclusion of these 3 systemic therapy regimens does not constitute an official recommendation for their use. Future versions of the guidelines could contain additional systemic therapy options and/or recommendations for patients with hereditary RCC, pending the availability of additional FDA-approved regimens and/or data supporting off-label use of existing regimens approved for treating RCC.

Conclusions

Emerging evidence informs panel recommendations in the NCCN Guidelines for Kidney Cancer and all other NCCN Guidelines. However, some treatment recommendations may also be informed by real-world clinical practice use and applicability in the absence of published data. Recent updates to the NCCN Guidelines for Kidney Cancer include new and restratified treatment option recommendations that may provide safer and more effective care for patients with kidney cancer. The panel also recently added new information on 7 of the most common hereditary RCC syndromes, and provides recommendations for genetic testing, screening, and/or treatment in patients who are suspected or confirmed to have one of these syndromes. This new section may help clinicians more effectively diagnose and manage patients with hereditary RCC, which is a complex and heterogeneous disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This activity is supported by educational grants from AstraZeneca; Celgene Corporation; Coherus BioSciences; Genentech, a member of the Roche Group; and TESARO, a GSK Company. This activity is supported in part by an educational grant from Bayer Healthcare Pharmaceuticals. This activity is supported by an independent medical education grant from Bristol-Myers Squibb. This activity is supported by a medical education grant from Exelixis, Inc. This activity is supported by an independent educational grant from Merck & Co., Inc.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7–30. [PubMed: 31912902]
2. 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. [PubMed: 10931460]
3. 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. [PubMed: 20171681]
4. 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. [PubMed: 25307281]
5. Maher ER. Hereditary renal cell carcinoma syndromes: diagnosis, surveillance and management. World J Urol 2018;36:1891–1898. [PubMed: 29680948]
6. Schmidt LS, Linehan WM. Genetic predisposition to kidney cancer. Semin Oncol 2016;43:566–574. [PubMed: 27899189]
7. National Cancer Institute: Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Kidney and Renal Pelvis Cancer. Accessed June 28, 2019. Available at: http://seer.cancer.gov/statfacts/html/kidrp.html
8. U.S. Food & Drug Administration. FDA approves pembrolizumab plus axitinib for advanced renal cell carcinoma. Accessed July 20, 2020. Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-plus-axitinib-advanced-renal-cell-carcinoma
9. Pembrolizumab. Prescribing information. Merck; 2014. Accessed July 20, 2020. Available at: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf
10. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380: 1116–1127. [PubMed: 30779529]
11. Lenvatinib. Prescribing information. Eisai; 2020. Accessed July 20, 2020. Available at: http://www.lenvima.com/pdfs/prescribing-information.pdf
12. U.S. Food & Drug Administration. FDA approves lenvatinib in combination with everolimus for advanced renal cell carcinoma. Accessed July 20, 2020. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/lenvatinib-combination-everolimus
13. 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. [PubMed: 26482279]
14. 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. [PubMed: 28410911]
15. Hutson TE, Michaelson MD, Kuzel TM, et al. A phase II study of lenvatinib plus everolimus in patients with advanced non-clear cell renal cell carcinoma (nccRCC) [abstract]. J Clin Oncol 2020;38(Suppl):Abstract 685.
16. 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. [PubMed: 25012257]
17. Rednam SP, Erez A, Druker H, et al. Von Hippel-Lindau and hereditary pheochromocytoma/paraganglioma syndromes: clinical features, genetics, and surveillance recommendations in childhood. Clin Cancer Res 2017;23:e68–75. [PubMed: 28620007]
18. Tufton N, Sahdev A, Akker SA. Radiological surveillance screening in asymptomatic succinate dehydrogenase mutation carriers. J Endocr Soc 2017;1:897–907. [PubMed: 29264540]
19. Eijkelenkamp K, Osinga TE, de Jong MM, et al. Calculating the optimal surveillance for head and neck paraganglioma in SDHB-mutation carriers. Fam Cancer 2017;16:123–130. [PubMed: 27573198]
20. Krueger DA, Northrup H. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013;49: 255–265. [PubMed: 24053983]

21. Menko FH, van Steensel MA, Giraud S, et al. Birt-Hogg-Dubé syndrome: diagnosis and management. Lancet Oncol 2009;10:1199–1206. [PubMed: 19959076]
22. Star P, Goodwin A, Kapoor R, et al. Germline BAP1-positive patients: the dilemmas of cancer surveillance and a proposed interdisciplinary consensus monitoring strategy. Eur J Cancer 2018;92:48–53. [PubMed: 29413689]
23. Ornstein DK, Lubensky IA, Venzon D, et al. Prevalence of microscopic tumors in normal appearing renal parenchyma of patients with hereditary papillary renal cancer. J Urol 2000;163:431–433. [PubMed: 10647647]
24. Pavlovich CP, Grubb RL III, Hurley K, et al. Evaluation and management of renal tumors in the Birt-Hogg-Dubé syndrome. J Urol 2005;173: 1482–1486. [PubMed: 15821464]
25. Shuch B, Singer EA, Bratslavsky G. The surgical approach to multifocal renal cancers: hereditary syndromes, ipsilateral multifocality, and bilateral tumors. Urol Clin North Am 2012;39:133–148. [PubMed: 22487757]
26. Gill AJ, Hes O, Papathomas T, et al. Succinate dehydrogenase (SDH)-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients. Am J Surg Pathol 2014; 38:1588–1602. [PubMed: 25025441]
27. Singer EA, Vourganti S, Lin KY, et al. Outcomes of patients with surgically treated bilateral renal masses and a minimum of 10 years of followup. J Urol 2012;188:2084–2088. [PubMed: 23083858]
28. Everolimus. Prescribing information. Novartis; 2020. Accessed July 20, 2020. Available at: https://www.novartis.us/sites/www.novartis.us/files/afinitor.pdf
29. Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2013;381:817–824. [PubMed: 23312829]
30. 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:Abstract 8.
31. Jonasch E, McCutcheon IE, Gombos DS, et al. Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-centre, phase 2 trial. Lancet Oncol 2018;19:1351–1359. [PubMed: 30236511]

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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.