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Release date: November 10, 2019; Expiration date: November 10, 2020

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Kidney Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Kidney Cancer

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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

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Kidney Cancer, Version 2.2020

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Kidney Cancer provide multidisciplinary recommendations for the clinical management of patients with clear cell and non–clear cell renal cell carcinoma, and are intended to assist with clinical decision-making. These NCCN Guidelines Insights summarize the NCCN Kidney Cancer Panel discussions for the 2020 update to the guidelines regarding initial management and first-line systemic therapy options for patients with advanced clear cell renal cell carcinoma.

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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.

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

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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.**

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Overview

In 2019, an estimated 73,820 people in the United States will be diagnosed with cancers of the kidney and renal pelvis, representing 4.2% of all new cancer diagnoses, and 14,770 will die of the disease.[1] Approximately 85% of kidney tumors are renal cell carcinoma (RCC), and approximately 70% are of clear cell histology.[2–4] Histologic diagnosis of RCC is established after surgical removal of renal tumors or after biopsy. For therapy selection, tumor histology, stage, and risk stratification of patients are important. Analysis of the SEER database indicates that RCC incidence has been stable and death rates have been falling on average 0.9% each year from 2007 through 2016.[5] Approximately 75% of patients with kidney cancer survive ≥5 years after diagnosis, with prognosis varying widely according to stage at diagnosis. Patients initially diagnosed with clinically localized RCC confined to the primary site have higher 5-year survival rates (92.5%), largely as a result of surgical interventions, compared with those initially diagnosed with distant cancer that has metastasized (12% alive at 5 years).[5]

2020 Updates to the NCCN Guidelines

Many issues were discussed during the panel meeting to update the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Kidney Cancer for 2020. Most notable were the impact of the results from the CARMENA trial on initial treatment options in select patients with stage IV disease[6] and the results from trials with novel immunotherapy combinations[9,33] (with either other immunotherapies or a tyrosine kinase inhibitor [TKI]) on first-line treatment options for advanced or relapsed stage IV clear cell renal cell carcinoma (ccRCC).

Initial Management of Stage IV Disease

Initial management for stage IV advanced RCC varies according to tumor resectability and prognostic risk factors. New for the 2020 guidelines, systemic therapy is the preferred initial treatment option for patients with stage IV disease who have any poor-risk features, clear cell histology, and high-volume distant metastases, instead of cytoreductive nephrectomy followed by systemic treatment (see KID-2, page 1281). This recommendation is based on results of the noninferiority phase III CARMENA trial, which included patients with biopsy-confirmed metastatic ccRCC who were suitable candidates for nephrectomy, eligible for treatment with sunitinib, had no brain metastases, and received no previous systemic treatment for kidney cancer.[6] Randomization was stratified according to intermediate- or poor-risk groups, in accordance with the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic model.[9] Many of the patients in the CARMENA trial had poor-risk features (44.4%) and a large burden of metastatic disease (median, 140 and 144 mm in nephrectomy/sunitinib and sunitinib-alone arms, respectively), underscoring the importance of patient selection to obtain the greatest benefit from nephrectomy prior to initiating systemic therapy with TKI agents such as sunitinib.[6,10] In the unstratified population, sunitinib alone was noninferior to sunitinib after nephrectomy, with a median overall survival (OS) of 18.4 versus 13.9 months, respectively (hazard ratio [HR], 0.89). Analysis by risk group also showed longer median OS for sunitinib alone compared with sunitinib after nephrectomy (intermediate-risk: 23.4 vs 19.0 months; HR for death, 0.92; 95% CI, 0.68–1.24, and poor-risk: 13.3 vs 10.2 months; HR for death, 0.86; 95% CI, 0.62–1.17).[6]

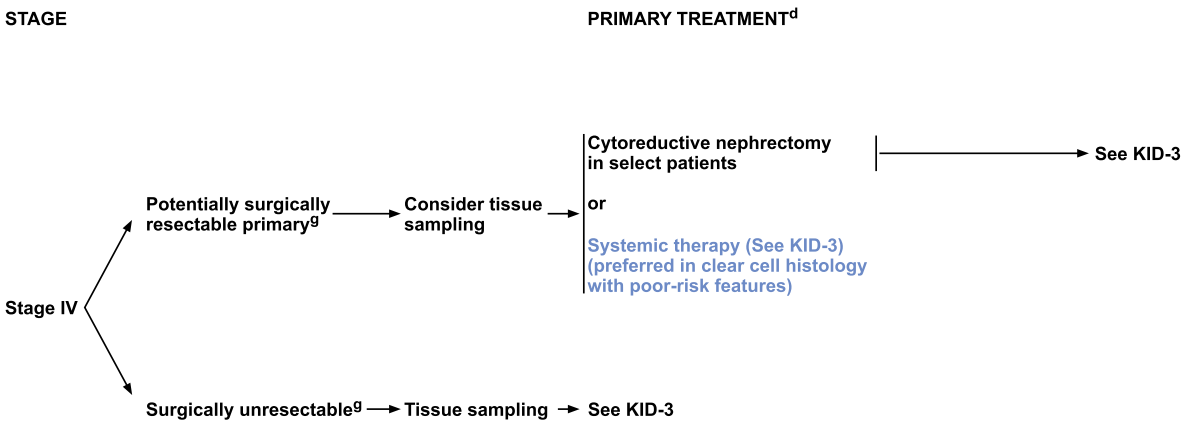
The role of cytoreductive nephrectomy in patients planned for treatment with frontline immunotherapy combinations remains to be clarified. Of significance, 80% of patients included in frontline immunotherapy combinations had prior nephrectomies.[7,11,12] Currently, results of the CARMENA trial support the general principle of initial systemic therapy for most patients with intermediate- and poor-risk disease.

Patients with excellent performance status and small-volume distant metastases could be considered for cytoreductive nephrectomy followed by systemic treatment. A subset of patients with a resectable primary RCC and synchronous oligometastatic disease can be managed with either surgical metastasectomy, stereotactic body radiation therapy,[13–15] or ablative techniques (see KID-3, page 1282). In patients with stage IV disease whose tumors are surgically unresectable, the panel recommends performing tissue sampling to determine histology and guide subsequent management.

Prognostic Risk Models

In addition to histology, the NCCN panel emphasized the use of prognostic risk models to guide treatment selection in clinical practice.[9,16] Prognostic scoring systems have been developed to define risk groups by combining independent prognostic factors for survival in patients with metastatic RCC. Prognostic models are important in clinical trial design to ensure correct treatment selection for patients. The 2 most common prognostic factor models are from MSKCC, using data from the cytokine era,[9] and the International Metastatic RCC Database Consortium (IMDC).[16] The IMDC criteria are more relevant to today's practice because they were developed in the era of targeted and immunomodulatory therapies.

The models identify 5 or 6 clinical parameters to stratify patients into low/favorable-, intermediate-, and poor-risk groups. Overlapping factors between the MSKCC and IMDC models include interval from diagnosis to treatment, Karnofsky performance status, and calcium and hemoglobin concentrations. The MSKCC model also uses lactate dehydrogenase levels, whereas the IMDC model uses



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

KID-2

neutrophil and platelet counts. Patients with none of the prognostic factors are considered to be low-risk or have good prognosis, those with 1 or 2 factors have intermediate-risk disease, and patients with ≥3 factors have poor-risk disease.

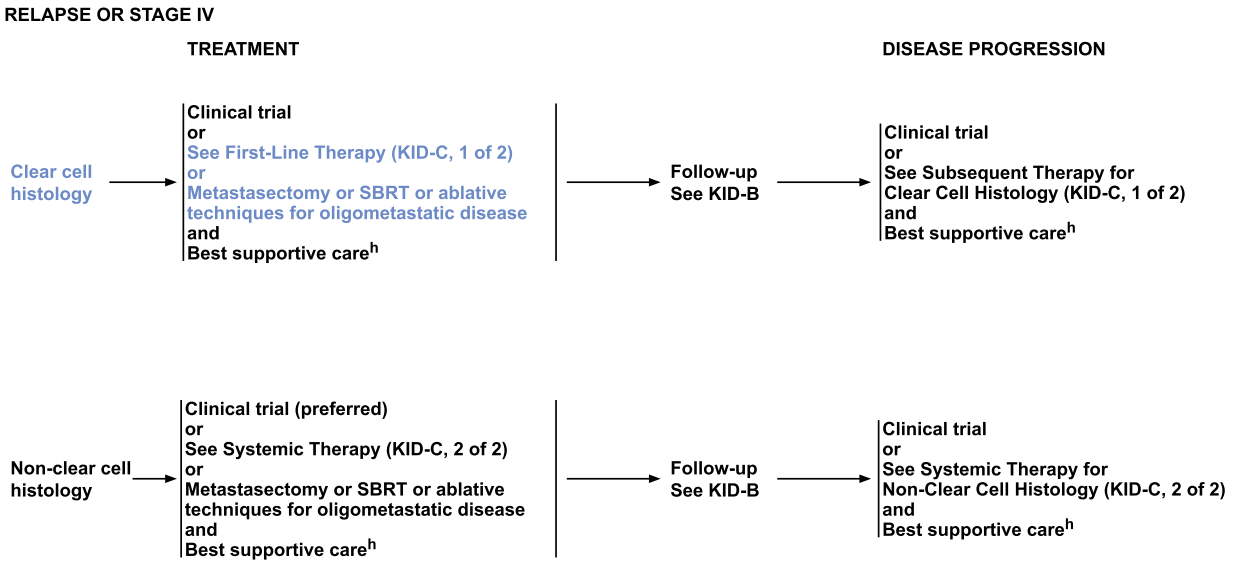
The IMDC criteria are used in the NCCN Guidelines to guide first-line therapy selection for patients with clear cell histology. Other factors shown to be important prognostic determinants of 5-year survival are tumor stage and grade, local extent of the tumor, presence of regional nodal metastases, and evidence of metastatic disease at presentation.[17–26] To further guide management of advanced RCC, the panel has categorized systemic RCC therapy regimens as "preferred," "other recommended," or "useful under certain circumstances." This categorization provides guidance on treatment selection by considering efficacy, safety, evidence, and other factors, including preexisting comorbidities, nature of the disease, and in some cases, consideration of access to agents.

First-Line Systemic Therapy for Relapsed or Stage IV ccRCC

Cytotoxic chemotherapy generally is not effective in advanced ccRCC. Systemic therapies with checkpoint inhibitor immunotherapies and targeted therapies have proven to be more effective, and are generally recommended for patients with evidence of metastases, after cytoreductive nephrectomy in patients with multiple metastatic sites, or for patients with surgically unresectable tumors.

The past 2 decades have broadened the selection of new first-line systemic therapies for patients with advanced ccRCC in terms of numbers and unique mechanisms of action, with an accelerated pace of approvals in the past few years. The only therapy remaining from the cytokine era for first-line treatment of ccRCC is high-dose IL-2, which is only used in highly selected patients at certain centers.[27,28] Targeted therapies that block angiogenesis were a part of the next era. Currently recommended first-line targeted therapy options in the NCCN Guidelines are single-agent TKIs or VEGF inhibitors, including pazopanib,[29] sunitinib,[30] axitinib,[31] and cabozantinib,[32] or temsirolimus, which targets mTOR.[33]

The introduction of immune checkpoint inhibitors that alter the interaction between immune cells and antigen-presenting cells, including tumor cells, changed the treatment landscape of RCC and launched the



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

KID-3

current era. The first approval for nivolumab monotherapy was in 2015, followed by approval of nivolumab + ipilimumab in 2018.[11] Nivolumab is an antibody that selectively blocks the interaction between PD-1 (expressed on activated T cells) and its ligands, PD-L1 and PD-L2 (expressed on antigen-presenting cells, including immune cells and tumor cells). Ipilimumab is an antibody that selectively blocks the interaction between the negative regulator CTLA-4 (expressed early on activated T cells) and its ligands CD80/CD86 (expressed on antigen-presenting cells). A new generation of approvals in 2019 resulted from merging antiangiogenic and antitumor immune response approaches, using the TKI axitinib combined with an immune checkpoint inhibitor—pembrolizumab[8] or avelumab.[7] Pembrolizumab is another antibody that blocks PD-1. Avelumab is an antibody that blocks PD-L1 (expressed on tumor cells and tumor-infiltrating immune cells) from interacting with its receptors. PD-1 and CD80 (found on T cells and antigen-presenting cells).

Updates to First-Line Treatment Options

At the 2020 update meeting, the panel discussed the success of 2 clinical trials with TKI and immunotherapy combination therapies.[7,8] KEYNOTE-426 is a phase III open-label trial that randomized 861 patients with previously untreated advanced ccRCC to receive axitinib + pembrolizumab versus sunitinib.[8] With a median follow-up of 12.8 months, median OS at 12 months was higher in the axitinib + pembrolizumab group compared with the sunitinib group (89.9% vs 78.3%; HR for death, 0.53; 95% CI, 0.38–0.74; $P<.0001$). Median progression-free survival (PFS) was 15.1 versus 11.1 months (HR for disease progression or death, 0.69; 95% CI, 0.57–0.84; $P<.001$). There was also an advantage in objective response rate (ORR; $P<.001$) for axitinib + pembrolizumab (59.3%; 95% CI, 54.5–63.9) over sunitinib (35.7%; 95% CI, 31.1–40.4). Grade ≥3 adverse events of any cause occurred in 75.8% of patients in the axitinib + pembrolizumab group and in 70.6% of those in the sunitinib group. OS and PFS by subgroup were included, and suggested an advantage for axitinib + pembrolizumab versus sunitinib for patients across IMDC risk groups in post hoc analysis. Based on these results, the NCCN panel has included axitinib + pembrolizumab as a category 1 preferred regimen option for first-line treatment of ccRCC in poor- and intermediate-risk patients, and a category 2A preferred regimen option for first-line treatment of ccRCC in favorable-risk patients.

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

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]

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.

KID-C
1 of 2

The phase III JAVELIN Renal 101 trial compared axitinib + avelumab versus sunitinib in 886 patients with previously untreated advanced ccRCC; most patients (63.2%) had PD-L1–positive tumors.[7] Primary endpoints were tested in the 560 patients with PD-L1–positive tumors, and study results showed improved PFS (13.8 vs 7.2 months; HR for disease progression or death, 0.61; 95% CI, 0.47–0.79; $P<.001$) and ORR (55.2% vs 25.5%) with axitinib + avelumab versus sunitinib, respectively. Median PFS in the unselected overall population was significantly better for patients treated with axitinib + avelumab versus sunitinib (13.8 vs 8.4 months, respectively; HR, 0.69; 95% CI, 0.56–0.84; $P<.001$). Grade ≥3 adverse events were comparable in the axitinib + avelumab versus sunitinib groups (71.2% vs 71.5%). OS results were not yet mature. Based on the available data and FDA approval, axitinib + avelumab are listed in the NCCN Guidelines as a category 2A other recommended option as first-line treatment across all risk groups for patients with previously untreated stage IV ccRCC.

Changing Treatment Landscape

The recommendation for including the TKI with immunotherapy combinations in the NCCN Guidelines prompted a discussion of the changing treatment landscape for first-line ccRCC. Historically, PFS was the primary efficacy endpoint used in the pivotal phase III trials of sunitinib[30] and pazopanib.[29] Both recent phase III TKI/immunotherapy combination studies[7,8] showed a PFS advantage over sunitinib, the previous standard of care, and pembrolizumab + axitinib showed an OS advantage. These results clearly decrease the strength of evidence supporting the use of sunitinib, and by extension, other VEGFR TKI monotherapies in the frontline setting. The recommendations for use of pazopanib and sunitinib were therefore changed from category 1 to category 2A for treatment of patients with ccRCC in the first-line setting.

The pivotal phase III studies of sunitinib[30] and pazopanib[29] had a majority of favorable- and intermediate-risk patients and a relatively small subset of poor-risk patients. For favorable-risk patients, because of the significant improvement in PFS and the OS benefit compared with sunitinib, the guideline lists axitinib + pembrolizumab, pazopanib, and sunitinib as category 2A preferred regimen options for patients with ccRCC. For intermediate- and poor-risk patients, there are higher-quality data from the more recent immunotherapy

combination studies. The extended follow-up data for ipilimumab + nivolumab continues to support its use compared with sunitinib for intermediate- or poor-risk patients, showing an improved OS at 30 months (60% vs 47%) and ORR (42% for ipilimumab + nivolumab; 95% CI, 37–47, vs 29% for sunitinib; 95% CI, 25–34; P=.0001).[34] Given the significant improvement in PFS and the OS benefit for intermediate- or poor-risk patients compared with sunitinib, the panel listed ipilimumab + nivolumab and axitinib + pembrolizumab as category 1 preferred treatment options. The open-label phase II CABOSUN trial included intermediate- and poor-risk patients based on IMDC criteria with advanced RCC who received first-line therapy with either cabozantinib or sunitinib.[31] Patients treated with cabozantinib showed a significantly increased median PFS (8.2 vs 5.6 months) and a significantly higher ORR (46% vs 18%) compared with those who received sunitinib. Based on these results, the panel reaffirmed cabozantinib as a category 2A preferred treatment option for first-line treatment of ccRCC in poor- or intermediate-risk patients.

The full list of recommended regimens and their categories of preference for treatment of ccRCC can be found on page 1283 (KID-C, 1 of 2).

Conclusions

Recent trials have changed standard practice for advanced kidney cancer and underscore the importance of patient selection and use of the IMDC prognostic risk model in both initial management and systemic therapy selection for ccRCC. These NCCN Guidelines Insights highlight important changes in the 2020 version of the NCCN Guidelines for Kidney Cancer specific to the systemic treatment landscape. The introduction of immunotherapies and immunotherapy/TKI combinations have given patients with ccRCC more options in the frontline treatment setting. Currently there are no prospective data defining the role of cytoreductive nephrectomy in patients who subsequently receive checkpoint antibody therapy, but studies performed in the context of sunitinib therapy, including the CARMENA study,[6] indicate that initial systemic therapy is the treatment of choice for most patients with intermediate- or poor-risk features. Future studies will better define the role of systemic therapy and surgical options in the rapidly evolving RCC treatment algorithm.

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