

NCCN Clinical Practice Guidelines in Oncology  
(NCCN Guidelines®)

# Kidney Cancer

Overall management of Kidney Cancer is described in the full NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer. Visit [NCCN.org](https://www.nccn.org) to view the complete library of NCCN Guidelines®.

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PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV  
(M1 OR UNRESECTABLE T4, M0) OR RELAPSED DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable <sup>a</sup>	<ul style="list-style-type: none"> <li>• Axitinib + pembrolizumab<sup>b</sup> (category 1)</li> <li>• Cabozantinib + nivolumab<sup>b,c</sup> (category 1)</li> <li>• Lenvatinib + pembrolizumab<sup>b</sup> (category 1)</li> <li>• Ipilimumab + nivolumab<sup>b,d</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib + avelumab<sup>b</sup></li> <li>• Cabozantinib (category 2B)</li> <li>• Pazopanib</li> <li>• Sunitinib</li> </ul>	<ul style="list-style-type: none"> <li>• Active surveillance<sup>1,2,3</sup></li> <li>• Axitinib (category 2B)</li> </ul>
Poor/ intermediate <sup>a</sup>	<ul style="list-style-type: none"> <li>• Axitinib + pembrolizumab<sup>b</sup> (category 1)</li> <li>• Cabozantinib + nivolumab<sup>b,c</sup> (category 1)</li> <li>• Ipilimumab + nivolumab<sup>b,d</sup> (category 1)</li> <li>• Lenvatinib + pembrolizumab<sup>b</sup> (category 1)</li> <li>• Cabozantinib</li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib + avelumab<sup>b</sup></li> <li>• Pazopanib</li> <li>• Sunitinib</li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib (category 2B)</li> </ul>

Footnotes:

<sup>a</sup> Risk Models to Direct Treatment (IMDC criteria or MSKCC Prognostic Model) (KID-E).

<sup>b</sup> NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

<sup>c</sup> Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

<sup>d</sup> Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

References:

<sup>1</sup> Rini BI, Dorr TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. *Lancet Oncol* 2016;17:1317-1324.

<sup>2</sup> Harrison MR, Costello BA, Bhavsar NA, et al. Active surveillance of metastatic renal cell carcinoma: Results from a prospective observational study (MaRCC). *Cancer* 2021;127:2204-2212.

<sup>3</sup> Bex A. Increasing the evidence for surveillance of metastatic renal cancer. *Cancer* 2021;127:2184-2186.

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

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV OR RELAPSED DISEASE

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)			
Immuno-oncology (IO) Therapy History Status	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
IO Therapy Naïve	• None	<ul style="list-style-type: none"> <li>• Axitinib + pembrolizumab<sup>b</sup></li> <li>• Cabozantinib</li> <li>• Cabozantinib + nivolumab<sup>b,c</sup></li> <li>• Everolimus + lenvatinib</li> <li>• Ipilimumab + nivolumab<sup>b,d</sup></li> <li>• Lenvatinib + pembrolizumab<sup>b</sup></li> <li>• Nivolumab<sup>b,c</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib</li> <li>• Everolimus</li> <li>• Pazopanib</li> <li>• Sunitinib</li> <li>• Tivozanib<sup>f</sup></li> <li>• Belzutifan (category 2B)</li> <li>• Bevacizumab<sup>g</sup> (category 2B)</li> <li>• Axitinib + avelumab<sup>b</sup> (category 3)</li> </ul>
Prior IO Therapy	• None	<ul style="list-style-type: none"> <li>• Axitinib</li> <li>• Belzutifan<sup>e</sup></li> <li>• Cabozantinib</li> <li>• Everolimus + lenvatinib</li> <li>• Tivozanib<sup>f</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib + pembrolizumab<sup>b</sup></li> <li>• Cabozantinib + nivolumab<sup>b,c</sup></li> <li>• Everolimus</li> <li>• Ipilimumab + nivolumab<sup>b,d</sup></li> <li>• Lenvatinib + pembrolizumab<sup>b</sup></li> <li>• Pazopanib</li> <li>• Sunitinib</li> <li>• Bevacizumab<sup>g</sup> (category 2B)</li> <li>• Axitinib + avelumab<sup>b</sup> (category 3)</li> </ul>

<sup>b</sup> NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

<sup>c</sup> Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

<sup>d</sup> Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

<sup>e</sup> This regimen is for patients who have received a programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

<sup>f</sup> For patients who received ≥2 prior systemic therapies.

<sup>g</sup> An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

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

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV  
(M1 OR UNRESECTABLE T4, M0)<sup>h</sup> OR RELAPSED DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY <sup>i</sup>		
Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> <li>• Clinical trial</li> <li>• Cabozantinib</li> <li>• Cabozantinib + nivolumab<sup>b,c</sup></li> <li>• Lenvatinib + pembrolizumab<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Erlotinib + bevacizumab<sup>g</sup> + for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated RCC (<u>HERED-RCC-D</u>)</li> <li>• Everolimus + lenvatinib</li> <li>• Nivolumab<sup>b,c</sup></li> <li>• Pembrolizumab<sup>b</sup></li> <li>• Sunitinib</li> </ul>	<ul style="list-style-type: none"> <li>• Axitinib</li> <li>• Everolimus + bevacizumab<sup>g</sup></li> <li>• Everolimus</li> <li>• Ipilimumab<sup>b</sup> + nivolumab<sup>b,d</sup> (category 2B)</li> </ul>

<sup>b</sup> NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

<sup>c</sup> Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

<sup>d</sup> Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

<sup>g</sup> An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

<sup>h</sup> For first-line only.

<sup>i</sup> 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. Gemcitabine + doxorubicin can also produce responses in renal medullary carcinoma (RMC) (Wilson NR, et al. Clin Genitourin Cancer 2021;19:e401-e408). Oral targeted therapies generally do not produce responses in patients with RMC; erlotinib + bevacizumab can produce responses even in heavily pretreated patients with RMC. Outside of clinical trials, platinum-based chemotherapy regimens should be the preferred first-line therapy for RMC.

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

KID-D  
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Please see full Important Safety Information and Prescribing Information for CABOMETYX® (cabozantinib).

# Indications and Important Safety Information Provided by Exelixis

## INDICATIONS

CABOMETYX® (cabozantinib), in combination with nivolumab, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

CABOMETYX is indicated for the treatment of patients with advanced RCC.

## IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS

**Hemorrhage:** CABOMETYX can cause severe and fatal hemorrhages. The incidence of Grade 3-5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3-4 hemorrhage and before surgery. Do not administer to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

**Perforations and Fistulas:** Fistulas, including fatal cases, and gastrointestinal (GI) perforations, including fatal cases, each occurred in 1% of CABOMETYX patients. Monitor for signs and symptoms, and discontinue CABOMETYX in patients with Grade 4 fistulas or GI perforation.

**Thrombotic Events:** CABOMETYX can cause arterial or venous thromboembolic event. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events have occurred. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events.

**Hypertension and Hypertensive Crisis:** CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. In CABINET (n=195), hypertension occurred in 65% (26% Grade 3) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with antihypertensive therapy or for hypertensive crisis.

**Diarrhea:** CABOMETYX can cause diarrhea and it occurred in 62% (10% Grade 3) of treated patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1; resume at a reduced dose.

**Palmar-Plantar Erythrodysesthesia (PPE):** CABOMETYX can cause PPE and it occurred in 45% of treated patients (13% Grade 3). Withhold CABOMETYX until PPE resolves or decreases to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

**Hepatotoxicity:** CABOMETYX in combination with nivolumab in RCC can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. Monitor liver enzymes before initiation of treatment and periodically. Consider more frequent

monitoring as compared to when the drugs are administered as single agents. Consider withholding CABOMETYX and/or nivolumab, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity.

**Adrenal Insufficiency:** CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

**Proteinuria:** Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria; resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

**Osteonecrosis of the Jaw (ONJ):** CABOMETYX can cause ONJ and it occurred in <1% of treated patients. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures. Withhold CABOMETYX for development of ONJ until complete resolution; resume at a reduced dose.

**Impaired Wound Healing:** CABOMETYX can cause impaired wound healing. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** CABOMETYX can cause RPLS. Perform evaluation for RPLS and diagnose by characteristic finding on MRI any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

**Thyroid Dysfunction:** CABOMETYX can cause thyroid dysfunction, primarily hypothyroidism, and it occurred in 19% of treated patients (0.4% Grade 3). Assess for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitor for signs and symptoms during treatment.

**Hypocalcemia:** CABOMETYX can cause hypocalcemia, with the highest incidence in DTC patients. Based on the safety population, hypocalcemia occurred in 13% of CABOMETYX patients (2% Grade 3 and 1% Grade 4).

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume CABOMETYX at a reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

**Embryo-Fetal Toxicity:** CABOMETYX can cause fetal harm. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

## ADVERSE REACTIONS

The most common (≥20%) adverse reactions are:

CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, and constipation.

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

## DRUG INTERACTIONS

**Strong CYP3A4 Inhibitors:** If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

**Strong or Moderate CYP3A4 Inducers:** If coadministration with strong or moderate CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

## USE IN SPECIFIC POPULATIONS

**Lactation:** Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

**Hepatic Impairment:** In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

[Please see accompanying full Prescribing Information.](#)

**You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.FDA.gov/medwatch](http://www.FDA.gov/medwatch) or call 1-800-FDA-1088.**