

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 RELAPSE OR STAGE IV DISEASE

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

^a Risk Models to Direct Treatment (IMDC criteria or MSKCC Prognostic Model) (KID-D).

^b NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

^c Rini BI, et al. Lancet Oncol 2016;17:1317-1324. Harrison MR, et al. Cancer 2021;127:2204-2212. Bex A. Cancer 2021;127:2184-2186.

^d Patients with excellent performance status and normal organ function.

^e The poor risk model used in the global advanced renal cell carcinoma (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 less than the lower limit of normal (LLN), corrected calcium >10 mg/dL, LDH >1.5 times the upper limit of normal (ULN), and metastasis in multiple organs. Hudes G, et al. N Engl J Med 2007;356:2271-2281.

Note: 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

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"> • Axitinib + pembrolizumab^b • Cabozantinib • Cabozantinib + nivolumab^b • Ipilimumab + nivolumab^b • Lenvatinib + everolimus • Lenvatinib + pembrolizumab^b • Nivolumab^b 	<ul style="list-style-type: none"> • Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib^g • Belzutifan (category 2B) • Bevacizumab^h (category 2B) • High-dose IL-2 for selected patients^d (category 2B) • Temezirolimus^e (category 2B) • Axitinib + avelumab^b (category 3)
Prior IO Therapy	• None	<ul style="list-style-type: none"> • Axitinib • Belzutifan^f • Cabozantinib • Lenvatinib + everolimus • Tivozanib^g 	<ul style="list-style-type: none"> • Axitinib + pembrolizumab^b • Cabozantinib + nivolumab^b • Everolimus • Ipilimumab + nivolumab^b • Lenvatinib + pembrolizumab^b • Pazopanib • Sunitinib • Bevacizumab^h (category 2B) • High-dose IL-2 for selected patients^d (category 2B) • Temezirolimus^e (category 2B) • Axitinib + avelumab^b (category 3)

^b NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

^d Patients with excellent performance status and normal organ function.

^e 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 >10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, et al. N Engl J Med 2007;356:2271-2281.

^f This regimen is for patients that have received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

^g For patients who received ≥2 prior systemic therapies.

^h An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY ⁱ		
Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> • Clinical trial • Cabozantinib 	<ul style="list-style-type: none"> • Lenvatinib + everolimus • Nivolumab^b • Nivolumab^b + cabozantinib • Pembrolizumab^b • Sunitinib 	<ul style="list-style-type: none"> • Axitinib • Bevacizumab^h • Bevacizumab^h + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated RCC (<u>HERED-RCC-D</u>) • Bevacizumab^h + everolimus • Erlotinib • Everolimus • Nivolumab^b + ipilimumab^b (category 2B) • Pazopanib • Temsirolimus^e (category 1 for poor-prognosis risk group; category 2A for other risk groups)

^b [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

^e 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 >10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, et al. N Engl J Med 2007;356:2271-2281.

^h An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

ⁱ 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.

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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: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

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. 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 with medical management; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX 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): PPE occurred in 45% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Hepatotoxicity: CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone.

Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

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. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

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): ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. 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, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

Impaired Wound Healing: Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX 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): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Thyroid Dysfunction: Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

Hypocalcemia: CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN.

In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients.

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

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment 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 CYP3A4 Inducers: If coadministration with strong 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 or call 1-800-FDA-1088.