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**NCCN Clinical Practice Guidelines in Oncology  
(NCCN Guidelines®)**

# Hepatobiliary Cancers

Overall management of Hepatobiliary Cancers from diagnosis through recurrence is described in the full NCCN Guidelines® for Hepatobiliary Cancers. Visit [NCCN.org](https://www.nccn.org) to view the complete library of NCCN Guidelines.

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**First-Line Systemic Therapy**

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> <li>• Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)<sup>a,b,c,1</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Sorafenib (Child-Pugh Class A [category 1] or B7)<sup>d,e,2,3</sup></li> <li>• Lenvatinib (Child-Pugh Class A only)<sup>4,5</sup> (category 1)</li> </ul>	<ul style="list-style-type: none"> <li>• Nivolumab<sup>b,6</sup> (if ineligible for tyrosine kinase inhibitors [TKIs] or other anti-angiogenic agents) (Child-Pugh Class A or B) (category 2B)</li> <li>• FOLFOX (category 2B)<sup>f</sup></li> </ul>

**Subsequent-Line Therapy<sup>g</sup> if Disease Progression<sup>h</sup>**

**Options**

- Regorafenib (Child-Pugh Class A only) (category 1)<sup>i,7</sup>
- Cabozantinib (Child-Pugh Class A only) (category 1)<sup>i,8</sup>
- Ramucirumab (AFP ≥400 ng/mL only) (category 1)<sup>i,9</sup>
- Lenvatinib (Child-Pugh Class A only)
- Sorafenib (Child-Pugh Class A or B7)<sup>d,e</sup>

**Other Recommended Regimens**

- Nivolumab (Child-Pugh Class A or B)<sup>b,j,10-12</sup>
- Nivolumab + ipilimumab (Child-Pugh Class A only)<sup>b,i,13</sup>
- Pembrolizumab (Child-Pugh Class A only)<sup>b,j,k,14</sup> (category 2B)

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

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

<sup>c</sup> Patients on atezolizumab + bevacizumab should have adequate endoscopic evaluation and management for esophageal varices within approximately 6 months prior to treatment or according to institutional practice and based on the assessment of bleeding risk.

<sup>d</sup> See Child-Pugh Score (HCC-C) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).

<sup>e</sup> Caution: There are limited safety data available for Child-Pugh Class B or C patients and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, et al. J Clin Oncol 2009;27:1800-1805). The impact of sorafenib on patients potentially eligible for transplant is unknown.

<sup>f</sup> There are limited data supporting the use of FOLFOX, and use of chemotherapy in the context of a clinical trial is preferred. (Qin S, et al. J Clin Oncol 2013;31:3501-3508).

<sup>g</sup> Larotrectinib and entrectinib are treatment options for patients with hepatocellular carcinoma that is NTRK gene fusion positive. (Drlon A, et al. N Engl J Med 2018;378:731-739; Doebele RC, et al. Lancet Oncol 2020;21:271-282.)

<sup>h</sup> There are no data to define optimal treatment for those who progress after first-line systemic therapy, other than sorafenib or nivolumab.

<sup>i</sup> The data reflect use on or after sorafenib in patients who previously tolerated sorafenib at a dose of at least 400 mg per day.

<sup>j</sup> For patients who have not been previously treated with a checkpoint inhibitor because there is a lack of data for subsequent use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.

<sup>k</sup> Consider if MSI-H HCC.

**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.

## Indication and Important Safety Information Provided by Exelixis

### INDICATIONS

CABOMETYX®(cabozantinib) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

CABOMETYX®(cabozantinib) is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

### 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 and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. 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 36% (17% 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. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

**Diarrhea:** Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

**Palmar-Plantar Erythrodysesthesia (PPE):** PPE occurred in 44% 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.

**Proteinuria:** Proteinuria was observed in 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. 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.

**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 is observed. 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.

**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 commonly reported (≥20%) adverse reactions are: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, vomiting, weight decreased, constipation, and dysphonia.

#### 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 by [clicking here](#).**

**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.**

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