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NCCN Clinical Practice Guidelines in Oncology
(NCCN Guidelines®)

Hepatocellular Carcinoma

Overall management of Hepatocellular Carcinoma from diagnosis through recurrence is described in the full NCCN Guidelines® for Hepatocellular Carcinoma. Visit NCCN.org to view the complete library of NCCN Guidelines.

NCCN National Comprehensive Cancer Network®

PRINCIPLES OF SYSTEMATIC THERAPY

First-Line Systemic Therapy

Preferred Regimens

- **Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)[a,b,c,1]**
- **Tremelimumab-actl + durvalumab (category 1)[b,2]**

Other Recommended Regimens

- **Sorafenib (Child-Pugh Class A [category 1] or B7)[d,e,3,4]**
- **Lenvatinib (Child-Pugh Class A only) (category 1)[5,6]**
- **Durvalumab (category 1)[b,2]**
- **Pembrolizumab (category 2B)[b,7]**

Useful in Certain Circumstances

- **Nivolumab (Child-Pugh Class B only)[b,8]**
- **Atezolizumab + bevacizumab (Child-Pugh Class B only)[9]**
- **For TMB-H tumors:**
  - **Nivolumab + ipilimumab (category 2B)[10]**

Subsequent-Line Systemic Therapy if Disease Progression[f,g,h]

Options

- **Regorafenib (Child-Pugh Class A only) (category 1)[11]**
- **Cabozantinib (Child-Pugh Class A only) (category 1)[12]**
- **Lenvatinib (Child-Pugh Class A only)**
- **Sorafenib (Child-Pugh Class A or B7)[d,e]**

Other Recommended Regimens

- **Nivolumab + ipilimumab (Child-Pugh Class A only)[b,i,13]**
- **Pembrolizumab (Child-Pugh Class A only)[b,i,j,14-16]**

Useful in Certain Circumstances

- **Ramucirumab (AFP ≥400 ng/mL and Child-Pugh Class A only) (category 1)[17]**
- **Nivolumab (Child-Pugh Class B only)[b,i,18-21]**
- **For MSI-H/dMMR tumors**
  - **Dostarlimab-gxly (category 2B)[b,i,k,22,23]**
- **For *RET* gene fusion-positive tumors:**
  - **Selpercatinib (category 2B)[24]**
- **For TMB-H tumors:**
  - **Nivolumab + ipilimumab (category 2B)[b,i,l,10]**

[a] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[b] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[c] 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.
[d] See Child-Pugh Score (HCC-C) and assess portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[e] Caution: There are limited safety data available for patients with Child-Pugh Class B or C liver function 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.
[f] Larotrectinib and entrectinib are treatment options for patients with hepatocellular carcinoma that is NTRK gene fusion positive. (Drilon A, et al. N Engl J Med 2018;378:731-739; Doebele RC, et al. Lancet Oncol 2020;21:271-282.)
[g] There are no comparative data to define optimal treatment after first-line systemic therapy.
[h] Principles of Molecular Testing (HCC-H).
[i] 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.
[j] Pembrolizumab is a recommended treatment option for patients with or without microsatellite instability-high (MSI-H) HCC. Pembrolizumab is FDA-approved for MSI-H tumors.
[k] Dostarlimab-gxly is a recommended treatment option for patients with MSI-H/mismatch repair deficient (dMMR) recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.
[l] For patients with disease refractory to standard therapies or who have no standard treatment options available.

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.

The National Comprehensive Cancer Network® (NCCN®) appreciates that supporting companies recognize NCCN's need for autonomy in the development of the content of NCCN resources. All NCCN Guidelines are produced completely independently. NCCN Guidelines are not intended to promote any specific therapeutic modality.

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National Comprehensive Cancer Network®

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Indication and Important Safety Information Provided by Exelixis

INDICATION

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. 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, occurred in CABOMETYX patients. Monitor for signs and symptoms and discontinue in patients with Grade 4 fistulas or GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. 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. 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 anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea may be severe. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): 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.

Proteinuria: 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): 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: 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): RPLS 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. Assess for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitor for signs and symptoms during treatment.

Hypocalcemia: 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 of the potential risk to fetus. Verify pregnancy status and advise use of effective contraception during treatment and for 4 months after 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.

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 Important Safety Information and 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.