Version 1.2025
March 20, 2025

NCCN Clinical Practice Guidelines in Oncology
(NCCN Guidelines®)

Hepatocellular Carcinoma

Overall management of Hepatocellular Carcinoma is described in the full NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatocellular Carcinoma. Visit NCCN.org to view the complete library of NCCN Guidelines®.

NCCN National Comprehensive Cancer Network®

PRINCIPLES OF SYSTEMIC THERAPY[a-d]

First-Line Systemic Therapy

Preferred Regimens

- **Atezolizumab[e] + bevacizumab (category 1)[f,g,h,1]**
- **Tremelimumab-actl + durvalumab (category 1)[f,i,2]**

Other Recommended Regimens

- **Durvalumab (category 1)[f,h,2]**
- **Lenvatinib (category 1)[3,4]**
- **Sorafenib (category 1)[5,6]**
- **Tislelizumab-jsgr (category 1)[f,h,7]**
- **Nivolumab + ipilimumab[f,i,j,8-11]**
- **Pembrolizumab (category 2B)[f,h,k,12-15]**

Useful in Certain Circumstances

- **None**

Subsequent-Line Systemic Therapy if Disease Progression[l,m]

Options

- **Cabozantinib (category 1)[16]**
- **Regorafenib (category 1)[17]**

Other Recommended Regimens

- **Consider Preferred and Other Recommended Regimens for First-Line Systemic Therapy above**

Useful in Certain Circumstances

- **Ramucirumab (AFP ≥400 ng/mL) (category 1)[18]**
- **Nivolumab[f,h,n,19-22]**
- **For MSI-H/dMMR tumors**
  - **Dostarlimab-gxly (category 2B)[f,h,o,23]**
- **For *RET* gene fusion-positive tumors:**
  - **Selpercatinib (category 2B)[24]**
- **For *NTRK* gene fusion-positive tumors[p]:**
  - **Entrectinib[25]**
  - **Larotrectinib[26]**
  - **Repotrectinib[27]**

[a] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[b] Order does not indicate preference.
[c] See Principles of Liver Functional Assessment (HCC-E) and assess portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[d] Caution: Therapies listed may have limited safety data available for CTP Class B or C liver function. Use with extreme caution in patients with elevated bilirubin levels. Consult the prescribing information for individual agents.
[e] Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to atezolizumab for intravenous infusion.
[f] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[g] 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.
[h] For patients who have not been previously treated with a checkpoint inhibitor when used as subsequent-line therapy because there is a lack of data for subsequent use of single agent immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[i] For patients who have not been previously treated with anti-CTLA4-based combinations when used as subsequent-line therapy.
[j] 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.
[k] 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 in the subsequent-line setting.
[l] Regimens with first-line data are reasonable to consider for subsequent-line treatment, if not previously used. There are no comparative data to define optimal treatment after first-line systemic therapy.
[m] Principles of Molecular Testing (HCC-J).
[n] 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.
[o] 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.
[p] *NTRK* gene fusion-positive tumors are extremely rare in HCC.

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

References on HCC-I 2 of 2

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.

The distribution of this flashcard is supported by Exelixis, Inc.

National Comprehensive Cancer Network®

EXE-0063-10 04/25 FC-EXE-0134-1225

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: 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.

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.

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 full Prescribing Information for additional Important Safety 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.