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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,b,c]

First-Line Systemic Therapy

Preferred Regimens

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

Other Recommended Regimens

- **Durvalumab (category 1)[f,2]**
- **Lenvatinib (category 1)[3,4]**
- **Sorafenib (category 1)[5,6]**
- **Tislelizumab-jsgr (category 1)[f,7]**
- **Pembrolizumab (category 2B)[f,8]**

Useful in Certain Circumstances

- **For *NTRK* gene-fusion positive tumors:**
  - **Repotrectinib (category 2B)[9]**

Subsequent-Line Systemic Therapy if Disease Progression[h,i,j]

Options

- **Cabozantinib (category 1)[12]**
- **Regorafenib (category 1)[13]**
- **Lenvatinib**
- **Sorafenib**

Other Recommended Regimens

- **Nivolumab + ipilimumab[e,k,14-16]**
- **Pembrolizumab[f,l,m,n,17-19]**

Useful in Certain Circumstances

- **Ramucirumab (AFP ≥400 ng/mL) (category 1)[20]**
- **Nivolumab[f,l,m,21-24]**
- **For MSI-H/dMMR tumors**
  - **Dostarlimab-gxly (category 2B)[f,l,m,o,25]**
- **For *RET* gene fusion-positive tumors:**
  - **Selpercatinib (category 2B)[26]**

[a] Order does not indicate preference.
[b] See Principles of Liver Functional Assessment (HCC-E) and assess portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[c] Caution: Therapies listed may have limited safety data available for Child-Pugh Class B or C liver function. Use with extreme caution in patients with elevated bilirubin levels. Consult the prescribing information for individual agents.
[d] 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.
[e] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[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] There are no comparative data to define optimal treatment after first-line systemic therapy.
[i] Principles of Molecular Testing (HCC-J).
[j] Larotrectinib and entrectinib are treatment options for patients with *NTRK* gene-fusion positive HCC.[10,11] Repotrectinib (category 2B) is a treatment option for patients with *NTRK* gene-fusion positive HCC that has progressed on a prior NTRK-targeted treatment.[9]
[k] For patients who have not been previously treated with a checkpoint inhibitor unless following atezolizumab + bevacizumab.
[l] There is a lack of data for subsequent use of single agent immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[m] For patients who have not been previously treated with a checkpoint inhibitor.
[n] 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.
[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.

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

References

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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.