

NCCN Clinical Practice Guidelines in Oncology  
(NCCN Guidelines®)

# Thyroid Carcinoma

Overall management of Thyroid Carcinoma is described in the full NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma. Visit [NCCN.org](https://www.nccn.org) to view the complete library of NCCN Guidelines®.

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PRINCIPLES OF SYSTEMIC THERAPY

Differentiated Thyroid Cancer (RAI-refractory papillary carcinoma, RAI-refractory follicular carcinoma, oncocytic carcinoma): Progressive and/or symptomatic disease		
Preferred regimen	Other recommended regimen	Useful in certain circumstances
Lenvatinib (category 1) <sup>a,b,c</sup>	Sorafenib (category 1) <sup>a,b,c</sup>	<ul style="list-style-type: none"> <li>• Cabozantinib if progression after lenvatinib and/or sorafenib (category 1 for papillary carcinoma; category 2A for follicular carcinoma and oncocytic carcinoma)</li> <li>• Dabrafenib/trametinib<sup>e</sup> for <i>BRAF</i> V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options</li> <li>• Pembrolizumab/lenvatinib if disease progression on lenvatinib</li> <li>• Pemetrexed/carboplatin if disease progression following prior treatment</li> <li>• <i>NTRK</i> gene fusion-positive advanced solid tumors               <ul style="list-style-type: none"> <li>▶ Entrectinib</li> <li>▶ Larotrectinib</li> <li>▶ Repotrectinib</li> </ul> </li> <li>• <i>RET</i> gene fusion-positive tumors               <ul style="list-style-type: none"> <li>▶ Pralsetinib</li> <li>▶ Selpercatinib<sup>d</sup></li> </ul> </li> <li>• Pembrolizumab<sup>g</sup> for TMB-H (≥10 [mut/Mb]) or for MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options</li> <li>• Consider if clinical trials or other systemic therapies are not available or appropriate<sup>f</sup>:               <ul style="list-style-type: none"> <li>▶ Axitinib</li> <li>▶ Everolimus</li> <li>▶ Pazopanib</li> <li>▶ Sunitinib</li> <li>▶ Vandetanib</li> <li>▶ Dabrafenib (if <i>BRAF</i> positive) (category 2B)</li> <li>▶ Vemurafenib (if <i>BRAF</i> positive) (category 2B)</li> </ul> </li> </ul>

<sup>a</sup> Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease.

<sup>b</sup> After consultation with neurosurgery and radiation oncology, data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.

<sup>c</sup> Tyrosine kinase inhibitor (TKI) therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

<sup>d</sup> Selpercatinib is also FDA approved for pediatric patients 2 years of age or older.

<sup>e</sup> Dabrafenib/trametinib could also be appropriate as a first-line therapy for patients with high-risk disease who are not appropriate for VEGF inhibitors.

<sup>f</sup> Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

<sup>g</sup> See the NCCN Guidelines for Immunotherapy-Related Toxicities for treatment of toxicity from immunotherapy.

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

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## Indication and Important Safety Information Provided by Exelixis

### INDICATION

CABOMETYX® (cabozantinib) is indicated for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible.

### 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.

**Pediatric Use:** Physeal widening has been observed in children with open growth plates when treated with CABOMETYX. Physeal and longitudinal growth monitoring is recommended in children (12 years and older) with open growth plates. Consider interrupting or discontinuing CABOMETYX if abnormalities occur. The safety and effectiveness of CABOMETYX in pediatric patients less than 12 years of age have not been established.

**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](http://www.FDA.gov/medwatch) or call 1-800-FDA-1088.**