

Thyroid Carcinoma, Version 2.2014

Featured Updates to the NCCN Guidelines

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Abstract

These NCCN Guidelines Insights focus on some of the major updates to the 2014 NCCN Guidelines for Thyroid Carcinoma. Kinase inhibitor therapy may be used to treat thyroid carcinoma that is symptomatic and/or progressive and not amenable to treatment with radioactive iodine. Sorafenib may be considered for select patients with metastatic differentiated thyroid carcinoma, whereas vandetanib or cabozantinib may be recommended for select patients with metastatic medullary thyroid carcinoma. Other kinase inhibitors may be considered for select patients with either type of thyroid carcinoma. A new section on “Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer” was added to the NCCN Guidelines to assist with using these novel targeted agents. (*J Natl Compr Canc Netw* 2014;12:1671–1680)

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Release date: December 12, 2014; Expiration date: December 12, 2015

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for Thyroid Carcinoma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Thyroid Carcinoma

Disclosure of Relevant Financial Relationships

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Supported by educational grants from Eisai, Inc.; Millennium: The Takeda Oncology Company; Teva Pharmaceuticals; Bayer HealthCare Pharmaceuticals Inc.; Celgene Corporation; Endo Pharmaceuticals and HealthTronics; Genentech; and ARIAD Pharmaceuticals, Inc.

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PRINCIPLES OF THYROID STIMULATING HORMONE (TSH) SUPPRESSION

- Because TSH is a trophic hormone that can stimulate the growth of cells derived from thyroid follicular epithelium, the use of levothyroxine to maintain low TSH levels is considered optimal in treatment of patients with papillary, follicular, or Hürthle cell carcinoma. However, data are lacking to permit precise specification of the appropriate serum levels of TSH.
- ▶ In general, patients with known **structural** residual carcinoma or at high risk for recurrence should have TSH levels maintained below 0.1 mU/L, whereas disease-free patients at low risk for recurrence should have TSH levels maintained either slightly below or slightly above the lower limit of the reference range.
- ▶ For low-risk patients with biochemical evidence but no structural evidence of disease (eg, Tg positive, but imaging negative), maintain TSH levels at 0.1 - 0.5 mU/L.
- ▶ Patients who remain disease free for several years can probably have their TSH levels maintained within the reference range.
- Given the potential toxicities associated with TSH-suppressive doses of levothyroxine---including cardiac tachyarrhythmias (especially in the elderly) and bone demineralization (particularly in post-menopausal women) as well as frank symptoms of thyrotoxicosis---the risk and benefit of TSH-suppressive therapy must be balanced for each individual patient.
- Patients whose TSH levels are chronically suppressed should be counseled to ensure adequate daily intake of calcium (1200 mg/day) and vitamin D (1000 units/day).

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THYR-A

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

In 2014, approximately 62,980 new cases of thyroid carcinoma will be diagnosed and approximately 1890 cancer deaths will occur from the disease in the United States.^{1,2} The main histologic types of thyroid carcinoma include (1) differentiated (including papillary, follicular, and Hürthle cell); (2) medullary (MTC); and (3) anaplastic (aggressive undifferentiated tumor). Of 55,554 patients diagnosed with thyroid carcinoma between 2007 and 2011, 88.0% had papillary carcinoma, 5.5% had follicular carcinoma, 2.3% had Hürthle cell carcinoma, 1.8% had MTC, and 0.9% had anaplastic carcinoma.³ Anaplastic thyroid carcinoma is almost uniformly lethal, but most thyroid carcinoma deaths are from papillary, follicular, or Hürthle cell carcinomas, which account for 95% of all thyroid carcinoma cases. However, most patients can be cured of differentiated thyroid carcinoma when properly treated by experienced physicians and surgeons,⁴ with a 5-year survival rate of 97.8%.³

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PRINCIPLES OF KINASE INHIBITOR THERAPY IN ADVANCED THYROID CANCER

- Oral kinase inhibitors demonstrate clinically significant activity in randomized, placebo controlled clinical trials in locally recurrent unresectable and metastatic medullary thyroid cancer (MTC) and in radio-iodine refractory differentiated thyroid cancer (DTC).^{1,2,3}
- When considering kinase inhibitor therapy for individual patients, several factors should be considered.
 - ▶ Kinase inhibitor therapy can be associated with progression free survival, but is not curative.
 - ▶ Kinase inhibitor therapy is expected to cause side effects that may have a significant effect on quality of life.
 - ▶ The natural history of MTC and DTC is quite variable with rates of disease progression ranging from a few months to many years.
- The pace of disease progression should be factored into treatment decisions. Patients with very indolent disease who are asymptomatic may not be appropriate for kinase inhibitor therapy, particularly if the side effects of treatment will adversely affect the patient's quality of life, whereas patients with more rapidly progressive disease may benefit from kinase inhibitor therapy, even if they have side effects.
- Optimal management of kinase inhibitor side effects is essential. Where available, guidelines outlining the management of the dermatologic, hypertensive and gastrointestinal side effects of kinase inhibitors can be used.^{4,5,6} In addition, dose modification can be considered, including dose holds and dose reductions.

¹Wells SA Jr, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012;30:134-141.

²Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomized, double-blind, phase 3 trial. *Lancet* 2014;384(9940):319-328.

³Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol* 2013;31:3639-3646.

⁴Burtneš B, Anadkat M, Basti S, et al. NCCN Task Force Report: Management of dermatologic and other toxicities associated with EGFR inhibition in patients with cancer. *J Natl Compr Canc Netw* 2009;7 Suppl 1:S5-S21.

⁵Brose MS, Frenette CT, Keefe SM, Stein SM. Management of sorafenib-related adverse events: a clinician's perspective. *Semin Oncol* 2014;41 Suppl 2:S1-S16.

⁶Carhill AA, Cabanillas ME, Jimenez C, et al. The noninvestigational use of tyrosine kinase inhibitors in thyroid cancer: establishing a standard for patient safety and monitoring. *J Clin Endocrinol Metab* 2013;98:31-42.

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THYR-B

Differentiated Thyroid Carcinoma

First-line preferred treatment for differentiated thyroid carcinoma is surgery, whenever possible, followed by radioactive iodine (RAI) in selected patients, and levothyroxine therapy in all patients (see THYR-A, page 1673).⁵ However, some patients have metastatic or recurrent disease that cannot be treated with surgery and/or is resistant to RAI. For patients with metastatic disease, the NCCN Thyroid Carcinoma Panel recommends individualized treatment based on tumor location, such as bone, central nervous system, or soft tissue (see PAP-9, page 1675). Although not curative, systemic and/or locoregional therapy may be recommended for patients with symptomatic and/or progressive disease that is not amenable to treatment with RAI.⁵⁻⁷

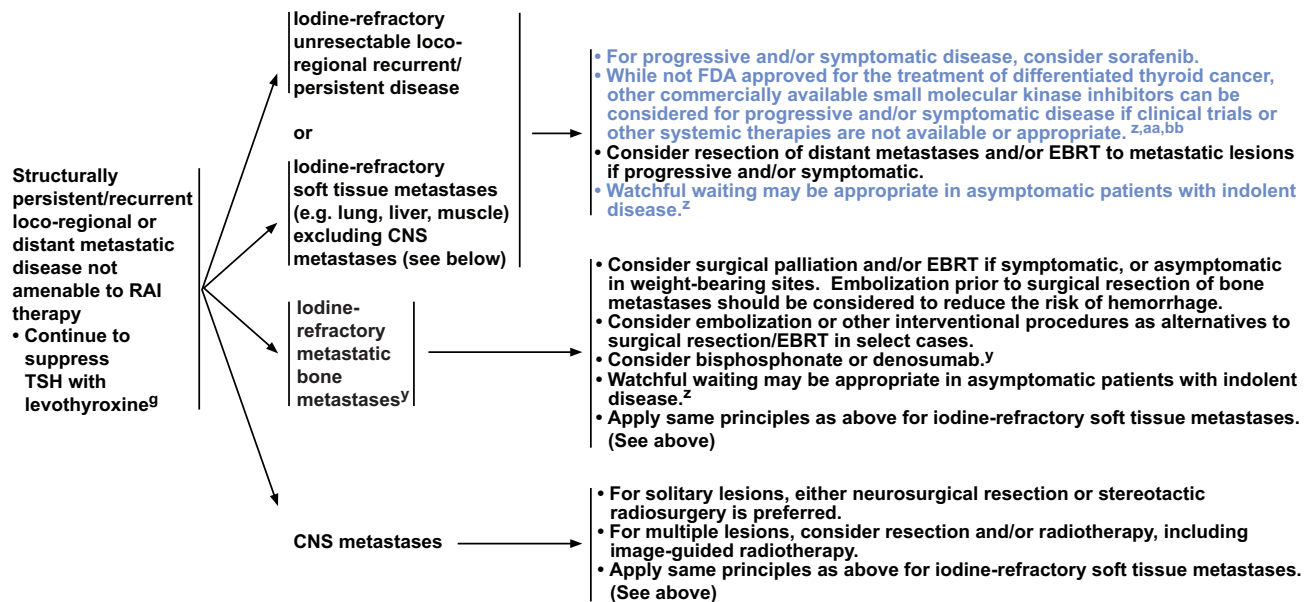
Systemic therapy includes kinase inhibitors, cytotoxic chemotherapy, and novel agents available on clinical trials. Treatment of locoregional disease depends on the site and includes external-beam ra-

diation therapy (EBRT), resection, stereotactic radiotherapy, and other therapies (see PAP-9, page 1675).^{5,8-13} Systemic therapy can be considered for tumors that are not surgically resectable, are not responsive to RAI, are not amenable to EBRT, and have shown clinically significant structural disease progression during the past 6 to 12 months.^{7,14}

Traditional cytotoxic systemic chemotherapy, such as doxorubicin, has minimal efficacy in patients with metastatic differentiated thyroid disease.^{15,16} Among 49 patients treated with 5 chemotherapy protocols, only 2 patients (3%) had objective responses.¹⁷ In a review of published series, 38% of patients had a response (defined as a decrease in tumor mass) to doxorubicin.¹⁸ Combination chemotherapy is not clearly superior to doxorubicin therapy alone.¹⁹ A recent study showed that targeted therapy of the MAP kinase pathway with selumetinib (an MEK inhibitor) significantly increased the effectiveness of RAI therapy in patients who were previously RAI-refractory.²⁰

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TREATMENT OF METASTATIC DIFFERENTIATED THYROID CARCINOMA NOT AMENABLE TO RAI THERAPY



⁹See Principles of TSH Suppression (THYR-A).

^yDenosumab and bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

^zKinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease.

See Principles of Kinase Inhibitor Therapy (THYR-B)

^{aa}While not FDA approved for treatment of differentiated thyroid cancer, commercially available small molecule kinase inhibitors (such as axitinib, pazopanib, sunitinib, or vandetanib [all are category 2A]) can be considered if clinical trials are not available or appropriate.

^{bb}Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

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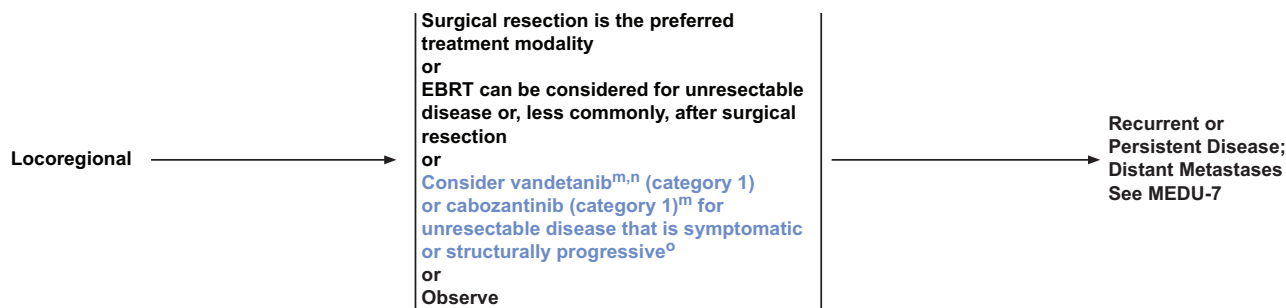
PAP-9

Kinase Inhibitors

Novel systemic therapies for patients with metastatic differentiated thyroid carcinoma have been evaluated.^{7,14,21–24} Multitargeted kinase inhibitors that are currently recommended in the NCCN Guidelines for Thyroid Carcinoma (to view the complete version, visit NCCN.org) for select patients with differentiated thyroid carcinoma include sorafenib,^{25–32} sunitinib,^{29,33} vandetanib,³⁴ pazopanib, and axitinib^{35,36} (see PAP-9, above).³⁷ For the 2014 update of the NCCN Guidelines, a new section on “Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer” was added to assist with using these novel targeted agents (see THYR-B, page 1674). This new section also pertains to patients with MTC. Other revisions to the recommended multikinase inhibitors are discussed in the following paragraphs. Novel agents under investigation include other multitargeted kinase inhibitors, such as lenvatinib, and BRAF (V600E) mutation inhibitors, such as vemurafenib.^{13,14,38–42}

Clinical trials suggest that kinase inhibitors have a clinical benefit (partial response rates plus stable disease) in 50% to 60% of patients, usually for approximately 12 to 24 months.^{14,29,37,43–45} Patients with rapidly progressive disease may benefit from kinase inhibitor therapy even if they experience side effects.⁷ Kinase inhibitor therapy may cause severe side effects, and therefore may not be appropriate for patients with stable or slowly progressive indolent disease.^{6,7,32,46} Watchful waiting may be appropriate for asymptomatic patients with indolent disease.⁴⁷ Severe or fatal side effects from kinase inhibitors include bleeding, hypertension, stroke, and liver toxicity; however, most side effects can be managed and are reversible with discontinuation of the drug.^{32,48–52} Dose modification and dose holds of the kinase inhibitors may enable patients to continue therapy (see the prescribing information). The dose of levothyroxine often needs to be increased in patients taking kinase inhibitors.^{46,47} Because some kinase inhibitors

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RECURRENT OR PERSISTENT MEDULLARY THYROID CARCINOMA
Locoregional disease

^mIncreasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.

ⁿOnly health care professionals and pharmacies certified through the vandetanib Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribution program, will be able to prescribe and dispense the drug.

^oKinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer (THYR-B).

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MEDU-6

are metabolized by cytochrome P450 isoenzymes, patients are at risk for drug-drug interactions.⁵³ Patients should be cautioned not to drink grapefruit juice if they are taking kinase inhibitors such as sunitinib, pazopanib, or axitinib.

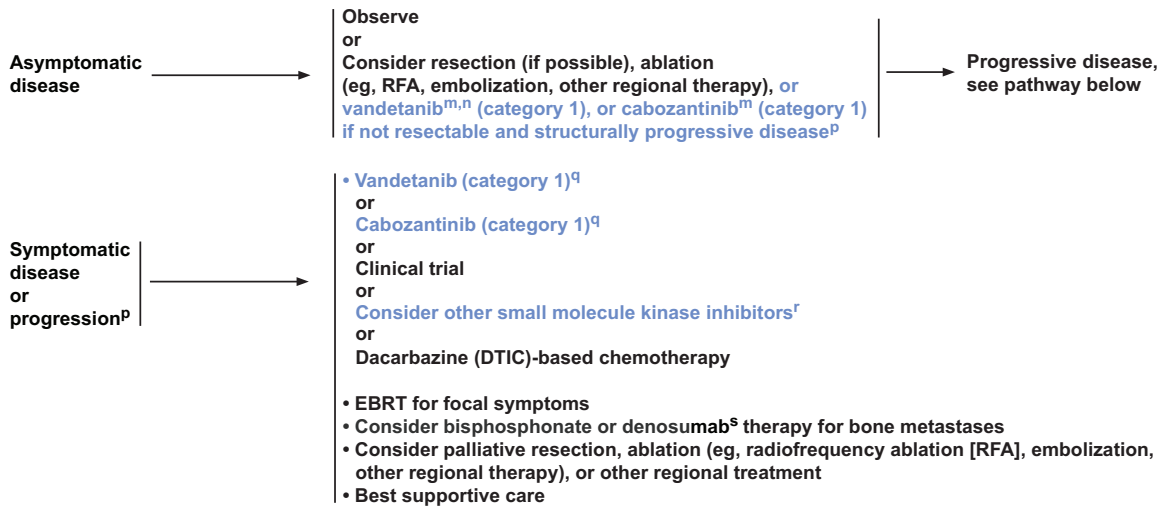
Kinase inhibitor therapy may be used to treat thyroid carcinoma that is symptomatic and/or progressive and not amenable to treatment with RAI. For the 2014 update, recommendations were revised for the use of kinase inhibitors. Sorafenib may be considered for select patients with differentiated thyroid carcinoma; other kinase inhibitors are also an option (see PAP-9, page 1675). Sorafenib may be considered for progressive and/or symptomatic differentiated thyroid carcinoma based on a recent phase III randomized trial and a recent FDA approval.^{25,32,54} For the 2014 update, sorafenib was from a footnote and into the algorithm based on this information (see PAP-9, page 1675).²⁵ If patients need to discontinue sorafenib because they have severe side ef-

fects, do not experience response to sorafenib, or experience progression on sorafenib, then other commercially available small molecule kinase inhibitors may also be considered, including pazopanib, sunitinib, vandetanib, or axitinib, although none have been approved by the FDA for differentiated thyroid cancer (see PAP-9, page 1675).⁵⁵⁻⁵⁷ For the 2014 update, vandetanib and axitinib were added to the footnote as additional recommended kinase inhibitors that may also be considered based on results from recent phase II trials.³⁴⁻³⁶ In addition, pazopanib was changed from a category 2B recommendation to a category 2A recommendation based on results of a phase II trial and on panel experience.³⁷

Medullary Thyroid Carcinoma

Surgery is the main treatment for MTC, because no curative systemic therapy for MTC is available, although kinase inhibitors may be recommended for

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**RECURRENT OR PERSISTENT MEDULLARY THYROID CARCINOMA
DISTANT METASTASES**

^mIncreasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.

ⁿOnly health care professionals and pharmacies certified through the vandetanib Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribution program, will be able to prescribe and dispense the drug.

^pKinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer (THYR-B).

^qClinical benefit can be seen in both sporadic and familial MTC.

^rWhile not FDA approved for treatment of medullary thyroid cancer, other commercially available small molecule kinase inhibitors (such as sorafenib or sunitinib) can be considered if clinical trials, vandetanib or cabozantinib are not available or appropriate, or if the patient progresses on vandetanib or cabozantinib.

^sDenosumab and bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

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MEDU-7

locally advanced and metastatic MTC that is structurally progressive (see MEDU-6 and MEDU-7, page 1676 and above, respectively).⁵⁸⁻⁶¹ MTC cells do not concentrate RAI, and MTC does not respond well to conventional cytotoxic chemotherapy. Therefore, iodine-131 imaging cannot be used, and RAI treatment is not effective in these patients. Postoperative levothyroxine is indicated for all patients; however, thyroid stimulating hormone (TSH) suppression is not appropriate because C cells lack TSH receptors. Thus, TSH should be kept in the normal range by adjusting the levothyroxine dose.⁶²

Kinase Inhibitors

Kinase inhibitors may be recommended for select patients with MTC who have recurrent or persistent disease that is unresectable and structurally progressive (see MEDU-6 and MEDU-7, page 1676 and above, respectively).⁶³⁻⁶⁵ Multitargeted kinase inhibitors that are currently recommended or may

be considered for select patients with MTC include vandetanib, cabozantinib, sorafenib, and sunitinib (see MEDU-6 and MEDU-7, page 1676 and above respectively). Vandetanib and cabozantinib are oral kinase inhibitors that increase progression-free survival (PFS) in patients with metastatic MTC.^{58,61,66-68}

The NCCN Thyroid Carcinoma Panel recommends vandetanib or cabozantinib (both are category 1) for select patients with MTC based on recent phase III trials and FDA approval.⁵⁸⁻⁶¹ Severe or fatal side effects from kinase inhibitors include bleeding, hypertension, and liver toxicity; however, many side effects can be managed.^{46,49,55,69} Because some patients may have indolent and asymptomatic disease, these agents may not be appropriate (see THYR-B, page 1674).⁶³ Locoregional therapies, such as resection, ablation, and EBRT, are also recommended for the treatment of MTC (see MEDU-6 and MEDU-7, page 1676 and above, respectively).^{62,65}

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Vandetanib is a multitargeted kinase inhibitor that inhibits RET, vascular endothelial growth factor receptor (VEGFR), and endothelial growth factor receptor.⁵⁸ In the phase III randomized ZETA trial for unresectable, locally advanced, or metastatic MTC (N=331), vandetanib increased PFS compared with placebo (hazard ratio [HR], 0.46; 95% CI, 0.31–0.69; $P < .001$); overall survival data are not yet available.⁵⁸ Vandetanib was FDA-approved for use in patients with locally advanced or metastatic MTC who are not eligible for surgery and whose disease is causing symptoms or growing.^{58,59} However, access to vandetanib is restricted through a Risk Evaluation and Mitigation Strategy (REMS) program because of potential cardiac toxicity⁶⁹; other adverse events may also occur.^{69,70}

Cabozantinib is a multitargeted kinase inhibitor that inhibits RET, VEGFR-2, and MET. In a recent phase III randomized trial (EXAM) for patients with locally advanced or metastatic MTC (N=330), cabozantinib increased median PFS compared with placebo (11.2 vs 4.0 months; HR, 0.28; 95% CI, 0.19–0.40; $P < .001$); overall survival data are not yet available.⁶¹ The FDA recently approved the use of cabozantinib for patients with progressive metastatic MTC.^{60,61,71,72} Rare adverse events with cabozantinib include severe bleeding and gastrointestinal perforations or fistulas; severe hemorrhage is a contraindication for use of this agent.⁶³ If disease progresses on vandetanib or cabozantinib, systemic chemotherapy can be administered using dacarbazine or combinations that include dacarbazine.^{62,73,74} EBRT can be used for focal symptoms. Bisphosphonate therapy or denosumab can be considered for bone metastases.^{75–77} Best supportive care is also recommended.

Sorafenib or sunitinib can be considered, although not FDA-approved for MTC, if vandetanib, cabozantinib, or clinical trials are not available or appropriate (see MEDU-6 and MEDU-7, pages 1676 and 1677, respectively).^{33,78–86} In patients with metastatic MTC, sorafenib reduces symptoms caused by hypercalcitonemia and metastases.^{78,80} Sunitinib was associated with clinical response in several case reports.^{81,85,86} Clinical trials are assessing the effectiveness of novel multitargeted therapies, such as pazopanib.⁸⁷

Summary

These NCCN Guidelines Insights focus on some of the major updates to the 2014 NCCN Guidelines for Thyroid Carcinoma. Kinase inhibitor therapy may be used to treat thyroid carcinoma that is symptomatic and/or progressive and not amenable to treatment with RAI. Sorafenib may be considered for select patients with metastatic differentiated thyroid carcinoma, whereas vandetanib or cabozantinib may be recommended for select patients with metastatic MTC. Other kinase inhibitors may be considered for select patients with either type of thyroid carcinoma. A new section on kinase inhibitors was added to the NCCN Guidelines to assist with using these novel targeted agents.

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Posttest Questions

1. A 55-year-old woman has recurrent papillary thyroid cancer that is progressive, symptomatic, and refractory to radioiodine. She started taking kinase inhibitor therapy but has recently been feeling very tired. Her only other medication is levothyroxine. Which of the following is the most appropriate course of action?
 - a. The dose of the kinase inhibitor should be decreased.
 - b. Check thyroid function tests.
 - c. The kinase inhibitor should be discontinued.
 - d. The dose of levothyroxine should be decreased.
 - e. Kinase inhibitor therapy should be stopped until her symptoms subside and then therapy can be resumed.
2. True or False: Levothyroxine therapy is recommended in patients who have had total thyroidectomy.
3. For patients with progressive and/or symptomatic thyroid carcinoma, which of the following treatments may be used?

1. Sorafenib may be considered for select patients with papillary thyroid carcinoma whose disease is rapidly progressive.
 2. Cabozantinib may be considered for select patients with anaplastic thyroid carcinoma whose disease is rapidly progressive.
 3. Vandetanib or cabozantinib can be considered for select patients with MTC whose disease is rapidly progressive.
 4. Imatinib may be considered as postoperative treatment for select patients with MTC whose disease is rapidly progressive.
- There is only one correct answer.
- a. 1 and 3
 - b. 2 and 3
 - c. 2 and 4
 - d. 1 and 4

