

# THYROID CARCINOMA TREATMENT REGIMENS (Part 1 of 2)

**Clinical Trials:** The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are provided only to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

## Primary Treatment<sup>1</sup>

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

### Papillary Carcinoma

If patient has distant metastases, extrathyroidal extension, tumor greater than 4cm in diameter, cervical lymph node metastases, prior radiation exposure (Category 2B), or bilateral nodularity:

- » Total thyroidectomy
- » Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease
- » Consider prophylactic central neck dissection (Category 2B)

If patient has no prior radiation exposure, no distant metastases, no cervical lymph node metastases, no extrathyroidal extension, and tumor is less than 4w cm in diameter:

- » Total thyroidectomy (Category 2B)
- OR**
- » Lobectomy + isthmusectomy (Category 2B)

Post-surgical therapy may include radioiodine treatment, external beam radiation therapy, or adjuvant radioiodine ablation.

For bone metastases, bisphosphonate or denosumab therapy may be considered.

### Follicular Carcinoma

Total thyroidectomy if invasive cancer, metastatic cancer, or patient preference, or lobectomy/isthmusectomy.

Post-surgical therapy may include radioiodine treatment, external beam radiation therapy, embolization of metastasis, adjuvant radioiodine ablation, clinical trial for progressive disease, small molecule kinase inhibitor (sorafenib, axitinib, pazopanib, sunitinib, or vandetanib), or systemic therapy if trial not available.

For bone metastases, options above and bisphosphonate or denosumab therapy may be considered.

### Hürthle Carcinoma

Total thyroidectomy if invasive cancer, metastatic disease, or patient preference.

Post-surgical therapy may include radioiodine treatment, adjuvant radioiodine ablation, or external beam radiation therapy.

For bone metastases, bisphosphonate or denosumab therapy may be considered.

For clinically progressive or symptomatic disease, consider surgical resection +/- external beam radiation therapy of metastasis, clinical trial for non-radioiodine-sensitive tumors, small molecular kinase inhibitor (lenvatinib, sorafenib, axitinib, pazopanib, sunitinib, or vandetanib), or systemic therapy.

### Medullary Carcinoma

Total thyroidectomy with therapeutic or adjuvant external beam radiation therapy.

Locoregional:

- » Surgical resection +/- external beam radiation therapy
- » Consider external beam radiation therapy
- » For unresectable disease that is symptomatic or structurally progressive, consider vandetanib 300mg orally once daily<sup>2</sup> or cabozantinib 140mg orally once daily (max 180mg daily)<sup>3</sup> until disease progression (Category 1)<sup>4,5</sup>

Symptomatic distant metastases:

- » Clinical trial is preferred
- » Vandetanib or cabozantinib (Category 1)<sup>3-5</sup>
- » Small molecular kinase inhibitor (sorafenib, axitinib, pazopanib, or sunitinib) if vandetanib or cabozantinib are not available, appropriate, or if disease progresses<sup>3-7</sup>
- » Dacarbazine (DTIC)-based chemotherapy<sup>8</sup>
- » External beam radiation therapy for focal symptoms
- » For bone metastases, bisphosphonate or denosumab therapy may be considered.

Asymptomatic, distant metastases

- » Observation or resection, ablation if structurally progressive disease

*continued*

# THYROID CARCINOMA TREATMENT REGIMENS (Part 2 of 2)

## Primary Treatment<sup>1</sup> (continued)

### Anaplastic Carcinoma

Locally resectable or unresectable local tumor +/- distant disease—clinical trial preferred.

Consider external beam radiotherapy and/or concurrent chemotherapy. (Concurrent chemoradiation regimens: paclitaxel/carboplatin, paclitaxel, cisplatin or doxorubicin<sup>9</sup>; Chemotherapy regimens: paclitaxel/carboplatin, paclitaxel<sup>10</sup> or doxorubicin<sup>11</sup>)

### Treatment of Metastatic Disease Not Amenable to RAI Therapy

For progressive and/or symptomatic, radioactive iodine-refractory papillary, follicular, or Hürthle carcinoma, consider lenvatinib 24mg orally once daily or sorafenib 400mg orally twice daily.<sup>12,13</sup>

### Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma

- 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 radioiodine-refractory differentiated thyroid cancer (DTC).<sup>15-17</sup>
- 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 drug-induced 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; side effects have been fatal.<sup>12,16-18</sup> In addition, dose modification may be required, including dose holds and dose reductions.

## References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Thyroid Carcinoma V.1.2016. Available at: <http://www.nccn.org>. Accessed September 22, 2016.
2. Caprelsa [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals, LP. 2011.
3. Cometriq [package insert]. San Francisco, CA: Exelixis Inc. 2012.
4. Schoffski, et al. An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib (XL 184) in medullary thyroid carcinoma (MTC) patients (pts) with documented RECIST progression at baseline [abstract]. *J Clin Oncol*. 2012;30(Suppl 15):Abstract 5508.
5. Traynor K. Cabozantinib approved for advanced medullary thyroid cancer. *Am J Health Syst Pharm*. 2013;70(2):88.
6. Ravaut A, et al. Efficacy of sunitinib in advanced medullary thyroid carcinoma: intermediate results of phase II THYSU. *Oncologist*. 2010;15(2):212-213.
7. Sherman SI. Advances in chemotherapy of differentiated epithelial and medullary thyroid cancers. *J Clin Endocrinol Metab*. 2009;94(5):1493-1499.
8. Nocera M, et al. Treatment of advanced medullary thyroid cancer with an alternating combination of doxorubicin-streptozotocin and 5 FU-dacarbazine. Groupe d'Etude des Tumeurs à Calcitonine (GETC). *Br J Cancer*. 2000;83(6):715-718.
9. Smallridge RC, et al. American thyroid association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid*. 2012;22(11):1104-1139.
10. Ain KB, et al. Treatment of anaplastic thyroid carcinoma with paclitaxel: phase 2 trial using ninety-six-hour infusion. Collaborative Anaplastic Thyroid Cancer Health Intervention Trials (CATCHIT) Group. *Thyroid*. 2000;10(7):587-594.
11. Shimaoka K, et al. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. *Cancer*. 1985;56(9):2155-2160.
12. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med*. 2015;372(7):621-30.
13. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med*. 2015;372(7):621-30.
14. Wells 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.
15. Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol*. 2013;31:3639-3646.
16. Burtness 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.
17. Brose 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.
18. Carhill 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.