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REVIEW

Clinical Utility of Cabozantinib in the Treatment of Locally Advanced or Metastatic Differentiated Thyroid Carcinoma: Patient Selection and Reported Outcomes

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Abstract: Treatment of differentiated thyroid cancer (DTC) is multidisciplinary and begins with surgical intervention. Often, radioactive iodine is used as the prototype targeted therapy to ablate any residual thyroid tissue or metastatic deposits. While these initial therapeutic modalities are often curative with no need for further treatment, many patients develop radioactive-iodine refractory (RAIR) disease. When patients present with progressive RAIR disease, they often require systemic therapy. Several multikinase inhibitors have been approved for treatment of DTC, with sorafenib and lenvatinib employed in frontline treatment settings since approvals in 2013 and 2015, respectively. While patients have benefited from such treatment, progression is inevitable, and until recently, there were no established second-line options. Cabozantinib was recently approved for treatment of patients with DTC who have progressed on either frontline sorafenib or lenvatinib. Molecular testing for driver mutations or gene fusions, such as *BRAF V600E* or *RET* or *NTRK* fusions, has become standard recommendations for RAIR DTC patients due to excellent treatment options with highly selective targeted therapies, most RAIR DTC patients do not harbor such aberrations or have so-called "undruggable" mutations, making rendering cabozantinib an attractive and feasible treatment option for many patients.

Keywords: thyroid cancer, differentiated thyroid cancer, targeted therapy, cabozantinib, patient outcomes

Introduction

The incidence of thyroid cancers has significantly increased over the last several decades, in part due to the frequent use of thyroid ultrasound diagnosing more cases of this disease. Despite the increase in incidence, the mortality of thyroid cancer has stayed relatively stable during this timeframe, suggesting an increase in diagnosis of early-stage disease.[1] The increase in incidence has now declined from 7% annually during the 2000s to 1.5% annually from 2011 to 2015. Based on SEER data, approximately 67% of the patients have localized disease, 28% of the patients have locally advanced (LA) disease (defined as direct extension of the tumor as well as involvement of regional lymph nodes), and 4% of the patients have distant disease at the time of diagnosis.[2] The overall 5-year survival rate for all thyroid cancers is 98%, though outcomes including survival highly depend on the type and stage of the disease. There are three main types of thyroid cancer: differentiated (>90% of all thyroid cancers and includes papillary, follicular, and Hürthle cell), medullary (4%), and anaplastic (2%).[1]

Differentiated thyroid cancer (DTC) arises from the follicular cells of the thyroid. About 80–85% of DTC is comprised of papillary thyroid cancer. Within the subset of papillary thyroid cancer, about 50–70% will harbor BRAF V600E mutations, about 7% with harbor RET mutations, and <5% will harbor NTRK mutations. About 10–15% of DTC is comprised of follicular thyroid cancer. Within the subset of follicular thyroid cancer, about 30–45% will harbor RAS mutations. About 3–5% of DTC is comprised of Hürthle cell thyroid cancer. The only well-documented etiologic factor

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for the development of DTC is radiation exposure, with the highest risk observed in children and young adults who were exposed to external RT for other cancers. However, more than 90% of DTCs are unrelated to radiation exposure. DTCs are usually asymptomatic for long periods of time and sometimes present as a solitary thyroid nodule. Familial papillary thyroid cancers tend to be more clinically aggressive. Papillary thyroid cancer typically recurs locally in regional lymph nodes, while follicular and Hürthle cell cancers typically recur distantly, particularly in the lungs and bones. Factors that have been shown to be associated with a worse prognosis include age >45 years-old, male sex, poorly differentiated histology, tumor size >1.5 cm, and extrathyroidal extension at the time of diagnosis.[3,4]

Overall, there is a lack of consensus regarding a unified definition of advanced DTC. For some groups such as otolaryngology, advanced disease indicates that the primary tumor is invasive, bulky, or not amenable to surgical resection. For endocrinologists, advanced disease may mean refractory to conventional radioactive iodine therapy. To groups such as medical oncologists, advanced DTC may mean that there is the presence of distant metastases. In the last decade, treatment advances have been made for those with DTC. These advances are vast and include things such as multi-kinase inhibitors and other targeted therapies as well as immunotherapy. Various processes have been utilized to look for molecular aberrations in these tumors, including polymerase chain reaction (PCR), reverse transcription (RT)-PCR, next-generation sequencing (NGS), immunohistochemistry, and liquid assays such as cell-free DNA or circulating tumor cells. Utilization of these tests vary markedly between providers and there are no current guidelines as to the optimal timing to obtain molecular information or which patients may benefit the most from such testing.[5] As with many other cancers, the expression of the programmed death-ligand 1 (PD-L1) has been studied as a potential prognostic biomarker and therapeutic target for patients with DTC. A meta-analysis demonstrated that PD-L1 expression may be predictive of a higher risk of earlier recurrence in patients with papillary thyroid cancer.[6] In this paper, we will discuss the current treatment paradigms in DTC as well as the role for the multi-kinase inhibitor cabozantinib in the treatment of DTC with a discussion of patient selection and outcomes.

DTC Initial Work-Up, Staging, and Management of Localized Disease

Pre-operative evaluation of DTC includes a neck ultrasound with evaluation of the central and lateral neck lymph nodes and a neck MRI or CT with contrast if there is clinical concern for more advanced disease. CT images including CT chest imaging can be considered if there is clinical concern for distant metastatic disease. The mainstay of treatment for this disease remains surgical intervention. Based on the size and extent of disease, various surgical approaches can be considered, including lobectomy, near-total thyroidectomy, or total thyroidectomy.[3]

Post-operative staging of DTC includes several factors. According to the eighth edition of the AJCC staging system, Stage I disease is defined as any patient ≤55 years-old with a tumor of any size without any distant metastasis or patients >55 years-old with tumors ≤4 cm that are confined to the thyroid without lymph node or distant metastasis. Stage II disease is considered for any patient ≤55 years-old with a tumor of any size with distant metastasis present and patients >55 years-old with tumors >4 cm and confined to the thyroid, or with gross extrathyroidal extension into the strap muscles, or tumors <4 cm with metastasis to the regional lymph nodes. Stage III disease is considered in patients who are >55 years-old with tumors of any size with gross extrathyroidal extension into subcutaneous tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve without distant metastasis. Stage IV disease is defined in patients who are >55 years-old with tumors of any size with gross extrathyroidal extension into prevertebral fascia, encasing major vessels, or the presence of distant metastasis.[7]

Radioactive iodine (RAI) should be given for DTC with iodine-avid disease. It is utilized to destroy normal residual thyroid tissue (in which case it is termed remnant ablation), presumed residual or metastatic disease (in which case it is termed adjuvant therapy), and known residual or metastatic disease (in which case it is termed targeted therapy). Low-risk disease is defined as tumors ≤4cm which are limited to the thyroid without lymph node or distant metastatic disease. RAI adjuvant therapy is considered for intermediate-risk disease, which is defined as aggressive papillary thyroid cancer and thyroid cancer histology such as tall cell, diffuse sclerosing, and insular variants. RAI adjuvant therapy should be recommended for high-risk disease, which is defined as tumors with gross extrathyroidal extension, incomplete tumor resection at the time of surgery, or distant metastasis. Dosing strategies for RAI are determined by the prognostic risk of the patient; typical dosing ranges from 50 to 75 mCi for remnant ablation after total thyroidectomy in low-risk patients,

100–150 mCi for adjuvant therapy to locoregional lymph nodes, and 150–250 mCi for targeted therapy of distant metastases. Cumulative dose-related risks associated with RAI therapy include salivary ductal damage, dental caries, nasolacrimal duct obstruction, and secondary malignancies.[3,8]

Thyroid suppression with levothyroxine is also an important aspect of DTC management. Thyroid hormone suppressive therapy to maintain the TSH <0.1mU/L is recommended for patients with high-risk disease. The TSH may be kept at lower ranges for those with intermediate- and low-risk disease.[3,8,9]

Serum thyroglobulin measurements should be done 6–12 months after initial therapy for surveillance of disease. If thyroglobulin is undetectable and ultrasound of the neck is normal, annual surveillance is sufficient for patients with low-risk disease. In general, active surveillance approaches include neck ultrasound, with inclusion of thyroid and lymph node regions, and measurement of serum thyroglobulin and TSH for monitoring.[9]

Initial Treatment of Radioactive Iodine-Refractory Disease

For patients with recurrent and/or metastatic DTC, treatment paradigms differ slightly. One treatment option is surgical excision for locoregional disease. Another option is RAI for iodine-avid disease. Typically, retreatment with RAI is the modality of choice if metastasis develops, as complete response to treatment has been observed in up to 45% of the patients with distant metastasis and is considered curable in this setting. Additionally, radiation and other local control techniques can play a role in the treatment of recurrent or metastatic DTC. This can include external beam radiation therapy, thermal ablation, ethanol ablation, or chemoembolization for patients who have single or few metastases.[10,11]

Once DTC no longer takes up iodine on scanning or patients have received a total maximum of 600 mCi of RAI, their disease is termed radioactive iodine-refractory (RAI-R).[12] For progressive and/or symptomatic RAI-refractory DTC, systemic therapy is more likely to be used over regional managements like surgery or radiation. Additionally, there are risks associated with repeated RAI therapy, including the development of hematologic malignancies such as AML and MDS.[13]

Current Systemic Therapy Guidelines in DTC

There any many FDA-approved options for systemic therapy in the treatment of DTC. One such option is lenvatinib, which is an oral inhibitor of VEGFR1-3, fibroblast growth factor receptors 1–4, platelet-derived growth factor-alpha, and RET and KIT proto-oncogenes. This approval was based on the Phase III placebo-controlled SELECT trial (NCT01321554).[14] The median PFS was 18.3 months in the lenvatinib arm and 3.6 months in the placebo arm. Another systemic therapy option is sorafenib, which is an oral inhibitor of VEGFR1-3 and Raf kinases, including BRAF. This approval was based on the phase III placebo-controlled DECISION trial (NCT00984282).[15] In this trial, 417 patients with locally advanced or metastatic thyroid cancer that was RAI-R and progressed within the last 14 months were randomly assigned to receive 400 mg of oral sorafenib twice daily or placebo. Patients who received sorafenib had an increase in median PFS from 5.8 months in the placebo arm to 10.8 months ($p<0.0001$). Patients who received placebo as a part of the trial were allowed to receive sorafenib if they had progression of disease; therefore, the median OS was not statistically significant due to this crossover effect. The disease control rate was 54% in the sorafenib arm and 38% in the placebo arm ($p<0.0001$).

There are also more highly selective targeted therapies for RAI-refractory DTC, which are only used after NGS has been obtained on the patient's tumor specimen or from their serum and a targetable mutation has been identified. These therapies include selpercatinib, pralsetinib, larotrectinib and entrectinib. Selpercatinib is a small-molecule RET kinase inhibitor which is only used for RET fusion-positive DTC. This approval was based on the multicenter phase I/II clinical trial LIBRETTO-001 (NCT03157128).[16] In this trial, prolonged ORR was noted, up to 100% in systemic therapy-naïve RET fusion-positive thyroid cancer, with the majority of responders demonstrating responses of at least 6 months. Pralsetinib is a small-molecular RET kinase inhibitor which is also only used for RET fusion-positive DTC. This approval was based on the multicenter ARROW trial (NCT03037385) in patients whose tumors had RET gene alterations.[17] Efficacy for patients with RET fusion-positive thyroid cancer was evaluated in 9 patients who had RAI-R disease. The ORR was 89% (95% CI: 46%, 82%). Eighty-four percent of patients had responses lasting 6 months or longer. Larotrectinib and entrectinib are selective inhibitors of neurotrophic receptor kinase (NTRK) and are used in the

treatment of NTRK-fusion solid tumors, including RAI-refractory DTC. These approvals were based on the LOXO-TRK -14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)[18] trials for larotrectinib and ALKA-372-001 (EudraCT 2012–000148-88), STARTRK-1 (NCT02097810), and STARTRK-2 (NCT02568267)[19] trials for entrectinib. The major efficacy outcome measures were ORR and response duration for these trials.

In general, lenvatinib and sorafenib are the first-line treatments of choice for radioiodine-refractory metastatic DTC in the absence of driver mutation where a highly selective agent could be utilized. Cabozantinib can be considered a second-line therapy for RAI-refractory DTCs after treatment with lenvatinib or sorafenib. Data from the COSMIC-311 phase III randomized trial showed promising results (NCT03690388).[20] In this trial, patients with RAI-R DTC who progressed on prior sorafenib or lenvatinib were randomized to cabozantinib versus placebo. The PFS for cabozantinib was not reached; the median PFS for placebo was 1.9 months (HR 0.22). Genetic profiling of tumors is important for patients with DTC, as this testing can further expand their treatment options. For patients with RET fusion-positive thyroid cancer which is RAI-R, treatment with selpercatinib or pralsetinib are also options. Some patients can harbor BRAF mutations, which may be amenable to treatment with dabrafenib or vemurafenib.[21,22] Cytotoxic chemotherapy does not have a role in the treatment of DTC.[9] Table 1 outlines the currently approved targeted agents in the systemic treatment of DTC.

Cabozantinib in the Treatment of Recurrent or Metastatic DTC

Cabozantinib is a small-molecule inhibitor of tyrosine kinases associated with RET, MET, VEGFR-1, VEGFR-2, VEGFR-3, KIT, FLT-3, AXL, and TIE-2. The inhibition of these various receptor tyrosine kinases results in the inhibition of intracellular signaling pathways which are involved in cell proliferation, growth, angiogenesis, as well as invasion and metastatic capability and maintenance of the tumor microenvironment. Cabozantinib has FDA approval for progressive, metastatic medullary thyroid cancer (MTC), advanced renal cell carcinoma, and for hepatocellular carcinoma following

Table 1 Approved Targeted Agents in the Systemic Treatment of DTC

Treatment	Molecular Target	Clinical Trial ID(s)
Lenvatinib	Multikinase inhibitor (VEGFR1–3, FGFR 1–4, PDGFRα, c-KIT, RET)	NCT01321554
Sorafenib	Multikinase inhibitor (VEGFR2–3, PDGFRβ, RAF)	NCT00984282
Sunitinib	Multikinase inhibitor (PDGFRα, β, VEGFR1–3, c-KIT, CSF-1R, FLT-3, RET)	NCT00668811
Axitinib	Multikinase inhibitor (VEGFR1–3, PDGFR, c-KIT)	NCT00828919
Everolimus	Multikinase inhibitor (mTOR, HIF-1)	NCT01118065
Vandetanib	Multikinase inhibitor (EGFR, VEGFR, RET, BRK, TIE-2, EPH, Src)	NCT01876784
Cabozantinib	Multikinase inhibitor (RET, MET, VEGRF1–3, KIT, FLT-3, AXL, TIE-2)	NCT03690388
Pazopanib	Multikinase inhibitor (VEGFR1–3, PDGFRα, β, FGFR1&3, c-KIT, Itk, Lck, c-Fms)	NCT00625846
Vemurafenib	BRAF	NCT01286753
Dabrafenib	(BRAF, CRAF)	NCT01723202
Larotrectinib	NTRK1–3	NCT02122913;NCT02637687; NCT02576431
Entrectinib	NTRK1–3, some ROS1, ALK	EudraCT2012–000148-88; NCT02097810; NCT02568267
Selpercatinib	RET	NCT03157128
Pralsetinib	RET	NCT03037385
Pembrolizumab	PD-1	NCT02973997

prior treatment with sorafenib. The dosage for medullary thyroid cancer is 140 mg PO daily, while for renal cell carcinoma and hepatocellular carcinoma, it is 60 mg PO daily. Potential toxicities include mild-to-moderate skin reactions including rash, dry skin, alopecia, erythema, changes in hair color, and hyperkeratosis.[23]

Cabozantinib and vandetanib are FDA-approved targeted agents for the treatment of patients with locally advanced MTC which is not amenable to surgical resection and for patients with metastatic disease.[9,24,25] MTC is commonly associated with mutations in the RET proto-oncogene, which is one of the targets of cabozantinib. There are no data which compare these two agents head-to-head; therefore, the choice of agent used first is dependent upon the adverse event profile. Cabozantinib was first approved in the treatment of progressive medullary thyroid cancer based on a randomized, double-blind, placebo-controlled phase III trial, called the Efficacy of XL184 (Cabozantinib) in Advanced Medullary Thyroid Cancer (EXAM) trial (NCT00704730).[26] In this trial, 330 patients were randomly assigned in a 2:1 design to receive cabozantinib 140 mg per day or placebo. There was a statistically significant increase in PFS noted in the cabozantinib arm; patients who received cabozantinib had a PFS of 11.2 months and patients who received placebo had a PFS of 4 months. It is important to note that dose reductions were necessary in 79% of the patients in this trial. Cabozantinib is considered a non-RET-specific targeted therapy for metastatic medullary thyroid cancer. In subgroup analysis of patients with RET M918T-positive disease, the medial overall survival was 44.3 months for cabozantinib versus 18.9 months for placebo.

During the most recent ASCO annual meeting in 2022, there were two important abstracts of interest regarding the role of cabozantinib in patients with RAI-R DTC who progressed after prior VEGFR-targeted therapy. In the first study, patients were randomized in a 2:1 fashion to cabozantinib 60 mg daily or placebo. Patients who were randomized to placebo could cross over to open-label cabozantinib if they were noted to have disease progression. In this study, 258 patients were randomized; 170 patients to cabozantinib and 88 to placebo. Of these patients, 150 had papillary thyroid cancer and 113 patients had follicular thyroid cancer, with both groups containing 5 patients who had both papillary and follicular thyroid cancers. Within the group of patients with follicular thyroid cancer, 63 patients had Hürthle cell and poorly differentiated variants. Median PFS was 9.2 months for the cabozantinib group and 1.9 months for the placebo group within those patients who had papillary thyroid cancer (HR 0.27, 95% CI 0.17–0.43) and median PFS was 11.2 months for the cabozantinib group and 2.6 months for the placebo group within those patients who had follicular thyroid cancer (HR 0.18, 95% CI 0.10–0.31). Median PFS was 11.1 months for cabozantinib and 1.9 months for placebo in patients with the more aggressive Hürthle cell and poorly differentiated variants (HR 0.12, 95% CI 0.05–0.27). This study is ongoing, but early conclusions are that cabozantinib has superior efficacy versus placebo in all histologic subtypes of DTC.[27] The second study was an extension of the previously published results of the Phase 3 COSMIC-311 trial (NCT03690388). Patients were randomized 2:1 to cabozantinib 60 mg daily or placebo. Patients who were randomized to placebo could cross over to open-label cabozantinib if they were noted to have disease progression. Patients must have received lenvatinib or sorafenib and progressed during or after treatment with one or two prior VEGFR inhibitors. In this study of 258 patients, 96 (37%) had received previous sorafenib alone, 102 (40%) had received prior lenvatinib alone, and 60 (23%) previously received both sorafenib and lenvatinib. Median PFS was 16.6 for the cabozantinib group versus 3.2 months in the placebo group in those who were treated with previous sorafenib alone (HR 0.13, 95% CI 0.06–0.26). Median PFS was 5.8 months versus 1.9 months in those who were treated with previous lenvatinib alone (HR 0.28, 95% CI 0.16–0.48). Median PFS was 7.6 months vs 1.9 months in those who were treated with previous sorafenib and lenvatinib (HR 0.27, 95% CI 0.13–0.54).[28] This study demonstrated that cabozantinib maintained superior PFS compared to placebo irrespective of previous treatment with lenvatinib and/or sorafenib. This is the first phase III study showing a clinical benefit of cabozantinib after receiving previous lenvatinib therapy in patients who have RAI-R DTC and lead to the approval of cabozantinib in this setting for treatment of DTC.

Active Clinical Trials with Cabozantinib in Thyroid Cancer

There are several ongoing studies of cabozantinib in DTC, some of which are still recruiting. Table 2 outlines ongoing clinical trials with cabozantinib in both differentiated and medullary thyroid cancer.

There are trials specifically looking at the role of cabozantinib in the treatment of DTC. One such early-phase trial is investigating the effect of cabozantinib or lenvatinib on weight and body composition in patients with metastatic endocrine cancers, including a cohort of patients with DTC (NCT02592356).[29] The COSMIC-311 study in which patients with RAI-R DTC who progressed on prior VEGF-inhibitor therapy with sorafenib or lenvatinib were randomized to cabozantinib versus placebo is still ongoing as well (NCT03690388).[20] There is an ongoing Phase II trial of cabozantinib for the treatment of RAI-R

Table 2 Ongoing Clinical Trials with Cabozantinib in Thyroid Cancer

Treatment	Indication	Trial Status	Clinical Trial ID
Cabozantinib vs placebo after VEGF therapy	RAI-R DTC	Active,not recruiting	NCT03690388
Cabozantinib	RAI-R DTC	Active,not recruiting	NCT02041260
Cabozantinib, nivolumab, and Ipilimumab after VEGF therapy	RAI-R DTC	Active,not recruiting	NCT03914300
Cabozantinib vs Lenvatinib	Metastatic endocrine cancers (including DTC)	Active,not recruiting	NCT02592356
Cabozantinib plus atezolizumab	LA or metastatic tumors (including DTC)	Active,not recruiting	NCT03170960
Cabozantinib plus atezolizumab	Advanced endocrine cancers (including DTC)	Recruiting	NCT04400474
Cabozantinib plus nivolumab	Advanced cancer (including DTC) and HIV	Recruiting	NCT04514484
Two doses of cabozantinib (60 vs 140 mg)	Metastatic MTC	Active,not recruiting	NCT01896479
Cabozantinib	Young patients with R/M rare tumors (including MTC)	Active,not recruiting	NCT02867592

DTC in the first-line setting (NCT02041260),[30] which will help to define the role in timing of adding cabozantinib to the treatment armamentarium for these patients. Another trial is testing the combination of cabozantinib with the PD-1 inhibitor nivolumab, and CTLA-4 inhibitor ipilimumab for patients with advanced DTC (NCT03914300).[31] A similar study is investigating the activity of cabozantinib in combination with the PD-L1 monoclonal antibody atezolizumab in patients with locally advanced or metastatic solid tumors, including a cohort of patients with DTC (NCT03170960).[32] There are interesting pre-clinical data on the combination of anti-VEGF therapy with immune checkpoint inhibitors (ICI) and their synergistic effect. Hypoxic tumor microenvironments limit the efficacy of cytotoxic therapies such as traditional chemotherapy. This abnormal tumor microenvironment is associated with increased infiltration of immunosuppressive cells, such as regulatory T-cells. Vascular normalization of the tumor by VEGF inhibition may enhance the delivery of immunotherapy and improve the efficacy of ICI by reprogramming the tumor microenvironment and allowing for immune cell infiltration and anti-tumor activity.[33,34]

There are two trials with cabozantinib in DTC which are actively recruiting at the time of this review. One of these is a trial of cabozantinib plus atezolizumab in advanced and progressive neoplasms of the endocrine system: the CABATEN study (NCT04400474),[35] which has a cohort of patients with DTC. The other trial is testing the combination of cabozantinib and nivolumab in patients with advanced cancer and HIV (NCT04514484),[36] with a cohort of patients enrolled with DTC.

There are several ongoing studies of cabozantinib in medullary thyroid cancer, which are active but no longer recruiting patients. The first is a study of cabozantinib in treating younger patients with recurrent, refractory, or newly-diagnosed sarcomas, Wilms tumors, or other rare tumors, including a MTC cohort (NCT02867592).[37] There is another ongoing study of two different doses of cabozantinib (60 vs 140 mg daily) in progressive metastatic MTC (EXAMINER, NCT01896479)[38] after the EXAM study found efficacy of cabozantinib in advanced MTC (NCT00704730).[26] Another trial of expanded access of cabozantinib in MTC (NCT01683110) has been approved for marketing.[39]

Conclusion

The therapeutic landscape of thyroid cancer has dramatically changed over the past decade, from the approval of several multikinase inhibitors so more recently the approval of various highly selective inhibitors targeting specific driver

mutations in different forms of thyroid cancer. Cabozantinib is unique in its profile of targeting medullary thyroid cancer *RET* mutations as well as with activity in differentiated thyroid cancer following progression of disease with treatment of other multikinase inhibitors. Investigations are ongoing both as single-agent cabozantinib trials as well as combination therapy, offering hope and optimism for future treatment options.

Disclosure

Dr Jessica L Geiger reports personal fees from Exelixis, Merck, Astellas, and Regeneron, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Sanabria A, Kowalski LP, Shah JP, et al. Growing incidence of thyroid carcinoma in recent years: factors underlying overdiagnosis. *Head Neck*. 2018;40(4):855–866. doi:10.1002/hed.25029
2. SEER. SEER program coding and staging manual 2023; 2023.
3. Watkinson J. Thyroid cancer: a comprehensive guide to clinical management. *Ann R Coll Surg Engl*. 2008;90(4):360. doi:10.1308/003588408X286026i
4. Porter A, Wong DJ. Perspectives on the treatment of advanced thyroid cancer: approved therapies, resistance mechanisms, and future directions. *Front Oncol*. 2020;10:592202. doi:10.3389/fonc.2020.592202
5. Shonka DC, Ho A, Chintakuntlawar AV, et al. American Head and Neck Society Endocrine Surgery Section and International Thyroid Oncology Group consensus statement on mutational testing in thyroid cancer: defining advanced thyroid cancer and its targeted treatment. *Head Neck*. 2022;44(6):1277–1300. doi:10.1002/hed.27025
6. Girolami I, Pantanowitz L, Mete O, et al. Programmed death-ligand 1 (PD-L1) Is a potential biomarker of disease-free survival in papillary thyroid carcinoma: a systematic review and meta-analysis of PD-L1 immunoexpression in follicular epithelial derived thyroid carcinoma. *Endocr Pathol*. 2020;31(3):291–300. doi:10.1007/s12022-020-09630-5
7. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/tumor-node-metastasis Staging System for differentiated and anaplastic thyroid cancer (eighth edition): what changed and why? *Thyroid*. 2017;27(6):751–756. doi:10.1089/thy.2017.0102
8. PubMed. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. Available from: https://pubmed.ncbi.nlm.nih.gov/26462967/. Accessed March 10, 2023.
9. Haddad RI, Nasr C, Bischoff L, et al. NCCN guidelines insights: thyroid carcinoma, version 2.2018. *J Natl Compr Canc Netw*. 2018;16(12):1429–1440. doi:10.6004/jnccn.2018.0089
10. Paz-Fumagalli R, Li X, Smallridge RC. Ethanol ablation of neck metastases from differentiated thyroid carcinoma. *Semin Intervent Radiol*. 2019;36(5):381–385. doi:10.1055/s-0039-1696651
11. Kiess AP, Agrawal N, Brierley JD, et al. External-beam radiotherapy for differentiated thyroid cancer locoregional control: a statement of the American Head and Neck Society. *Head Neck*. 2016;38(4):493–498. doi:10.1002/hed.24357
12. Aashiq M, Silverman DA, Na'ara S, Takahashi H, Amit M. Radioiodine-refractory thyroid cancer: molecular basis of redifferentiation therapies, management, and novel therapies. *Cancers*. 2019;11(9):1382. doi:10.3390/cancers11091382
13. Molenaar RJ, Sidana S, Radivoyevitch T, et al. Risk of hematologic malignancies after radioiodine treatment of well-differentiated thyroid cancer. *J Clin Oncol*. 2018;36(18):1831–1839. doi:10.1200/JCO.2017.75.0232
14. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med*. 2015;372(7):621–630. doi:10.1056/NEJMoa1406470
15. Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet*. 2014;384(9940):319–328. doi:10.1016/S0140-6736(14)60421-9
16. Wirth LJ, Sherman E, Robinson B, et al. Efficacy of selpercatinib in RET-altered thyroid cancers. *N Engl J Med*. 2020;383(9):825–835. doi:10.1056/NEJMoa2005651
17. Subbiah V, Hu MI, Wirth LJ, et al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, Phase 1/2 study. *Lancet Diabetes Endocrinol*. 2021;9(8):491–501. doi:10.1016/S2213-8587(21)00120-0
18. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med*. 2018;378(8):731–739. doi:10.1056/NEJMoa1714448
19. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials. *Lancet Oncol*. 2020;21(2):271–282. doi:10.1016/S1470-2045(19)30691-6
20. Brose MS, Robinson B, Sherman SI, et al. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2021;22(8):1126–1138. doi:10.1016/S1470-2045(21)00332-6
21. Brose MS, Cabanillas ME, Cohen EEW, et al. Vemurafenib in patients with BRAF(V600E)-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multicentre, open-label, Phase 2 trial. *Lancet Oncol*. 2016;17(9):1272–1282. doi:10.1016/S1470-2045(16)30166-8
22. Busaidy NL, Konda B, Wei L, et al. Dabrafenib versus dabrafenib + trametinib in BRAF-mutated radioactive iodine refractory differentiated thyroid cancer: results of a randomized, phase 2, open-label multicenter trial. *Thyroid*. 2022;32(10):1184–1192. doi:10.1089/thy.2022.0115
23. Chu E, Jr VTD. *Physicians' Cancer Chemotherapy Drug Manual 2021*. Jones & Bartlett Learning; 2020.
24. Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol*. 2013;31(29):3639–3646. doi:10.1200/JCO.2012.48.4659
25. Fallahi P, Di bari F, Ferrari SM, et al. Selective use of vandetanib in the treatment of thyroid cancer. *Drug Des Devel Ther*. 2015;9:3459–3470. doi:10.2147/DDDT.S72495

26. Schlumberger M, Elisei R, Müller S, et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. *Ann Oncol*. 2017;28(11):2813–2819. doi:10.1093/annonc/mdx479
27. Capdevila J, Robinson B, Sherman SI, et al. Cabozantinib versus placebo in patients (pts) with radioiodine-refractory (RAIR) differentiated thyroid cancer (DTC) who progressed after prior VEGFR-targeted therapy: outcomes in prespecified subgroups based on histology subtypes. *JCO*. 2022;40 (16_suppl):6081. doi:10.1200/JCO.2022.40.16_suppl.6081
28. Hernando J, Capdevila J, Robinson B, et al. Cabozantinib (C) versus placebo (P) in patients (pts) with radioiodine-refractory (RAIR) differentiated thyroid cancer (DTC) who have progressed after prior VEGFR-targeted therapy: outcomes in prespecified subgroups based on prior VEGFR-targeted therapy. *JCO*. 2022;40(16_suppl). doi:10.1200/JCO.2022.40.16_suppl.6083
29. ClinicalTrials.gov. Effect of cabozantinib S-malate or lenvatinib mesylate on weight and body composition in patients with metastatic endocrine cancer - full text view. Available from: https://clinicaltrials.gov/ct2/show/NCT02592356. Accessed March 10, 2023.
30. Thomas Jefferson University. A phase II trial of cabozantinib for the treatment of radioiodine (RAI)-refractory differentiated thyroid carcinoma (DTC) in the first-line setting. clinicaltrials.gov; 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT02041260. Accessed March 10, 2023.
31. National Cancer Institute (NCI). Phase II study of XL184 (Cabozantinib) in combination with nivolumab and ipilimumab (CaboNivoIpi) in patients with radioiodine-refractory differentiated thyroid cancer whose cancer progressed after one prior VEGFR-targeted therapy. clinicaltrials.gov; 2023. Available from: https://clinicaltrials.gov/ct2/show/NCT03914300. Accessed March 10, 2023.
32. Exelixis. A Phase 1b dose-escalation study of cabozantinib (XL184) administered alone or in combination with atezolizumab to subjects with locally advanced or metastatic solid tumors. clinicaltrials.gov; 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT03170960. Accessed March 10, 2023.
33. Yi M, Jiao D, Qin S, Chu Q, Wu K, Li A. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. *Mol Cancer*. 2019;18:60. doi:10.1186/s12943-019-0974-6
34. Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev Clin Oncol*. 2018;15(5):325–340. doi:10.1038/nrclinonc.2018.29
35. Grupo Espanol de Tumores Neuroendocrinos. Exploratory basket trial of cabozantinib plus atezolizumab in advanced and progressive neoplasms of the endocrine system. CABATEN Study. clinicaltrials.gov; 2023. Available from: https://clinicaltrials.gov/ct2/show/NCT04400474. Accessed March 10, 2023.
36. National Cancer Institute (NCI). Pilot trial of nivolumab plus cabozantinib for advanced solid tumors in patients with HIV infection. clinicaltrials.gov; 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT04514484. Accessed March 10, 2023.
37. National Cancer Institute (NCI). Phase 2 Trial of XL184 (Cabozantinib) an oral small-molecule inhibitor of multiple kinases, in children and young adults with refractory sarcomas, Wilms tumor, and other rare tumors. clinicaltrials.gov; 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT02867592. Accessed March 10, 2023.
38. Exelixis. A randomized, double-blind study to evaluate the efficacy and safety of cabozantinib (XL184) at 60 mg/day compared to a 140 mg/day in progressive, metastatic medullary thyroid cancer patients. clinicaltrials.gov; 2023. Available from: https://clinicaltrials.gov/ct2/show/NCT01896479. Accessed March 10, 2023.
39. Exelixis. An open-label, expanded access study of cabozantinib (XL184) in subjects with unresectable, locally advanced, or metastatic medullary thyroid cancer. clinicaltrials.gov; 2013. Available from: https://clinicaltrials.gov/ct2/show/NCT01683110. Accessed March 10, 2023.