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Progressive Differentiated Thyroid Cancer: Best Use of the Tyrosine Kinase Inhibitors

Moderator



Marcia S. Brose, MD, PhD
Director, Center for Rare Cancers and Personalized Therapy
Abramson Cancer Center
Associate Professor
Department of Otorhinolaryngology, Head and Neck Surgery
Department of Medicine, Division of Hematology and Oncology
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Discussant



R. Michael Tuttle, MD
Clinical Director, Endocrine Service
Memorial Sloan Kettering Cancer Center
New York, New York
Professor of Medicine
Weill Medical College of Cornell University
New York, New York

Abstract: Thyroid cancer has one of the best overall survival rates among all malignancies, but it has a high incidence. There are various subtypes of thyroid cancer. The most common subtype is differentiated thyroid cancer (DTC), which responds well to treatment. The initial approach for DTC is surgery followed, in some cases, by adjuvant radioactive iodine (RAI) therapy. The decision to use adjuvant therapy is driven primarily by an assessment of the patient's risk of recurrence. A subset of patients develop RAI-refractory progressive DTC. Treatment options for these patients were relatively limited until the US Food and Drug Administration approved the tyrosine kinase inhibitors (TKIs) sorafenib and lenvatinib. These therapies improved progression-free survival in phase 3 trials. Incorporation of sorafenib and lenvatinib into the management plan has raised several questions, such as when to initiate treatment, how to sequence these agents, and how to prevent or manage adverse events, such as hand-foot reaction. Most patients with RAI-refractory, progressive DTC will ultimately receive treatment with both sorafenib and lenvatinib, regardless of which therapy is started first. Some data from the clinical trials can be used to guide sequencing in certain cases. Ongoing clinical trials are evaluating the TKIs in combination with other therapies, such as the mammalian target of rapamycin inhibitor everolimus.

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Initial Treatment of Progressive Differentiated Thyroid Cancer

R. Michael Tuttle, MD
 Clinical Director, Endocrine Service
 Memorial Sloan Kettering Cancer Center
 New York, New York
 Professor of Medicine
 Weill Medical College of Cornell University
 New York, New York

From a clinical perspective, the common types of thyroid cancers can be divided into 3 groups. The largest group consists of differentiated thyroid cancers (DTC), which arise from thyroid follicular cells and include papillary, follicular, and Hürthle cell thyroid cancers. Papillary carcinoma accounts for 80% of thyroid cancers, whereas follicular carcinoma and Hürthle cell carcinoma account for 10% and 3% of thyroid cancers, respectively. Papillary carcinomas are usually slow-growing thyroid cancers and have the best prognosis among the DTCs. The prognosis for patients with follicular or Hürthle cell carcinoma is also very good in most cases.^{1,2}

The second group of tumors, representing approximately 4% of thyroid cancers, are classified as medullary thyroid carcinomas. They arise from the neuroendocrine cells (referred to as the C cells) of the thyroid gland. This tumor type does not absorb radioactive iodine (RAI) and does not respond to thyroid-stimulating hormone (TSH) suppression therapy, both common treatments for DTC. Although the prognosis for intrathyroidal medullary thyroid cancer is very good, a worse prognosis can be seen in patients with distant metastases.

The third subgroup consists of the anaplastic carcinomas, an undifferentiated form of the tumor which also arises from thyroid follicular cells. This rare and aggressive form of thyroid cancer accounts for just 2% of all cases. It spreads quickly and is difficult to treat, and is therefore associated with a poor prognosis.^{1,2}

In 2015, an estimated 62,450 new cases of thyroid cancer were diagnosed, accounting for 3.8% of all new cancer cases. Thyroid cancer ranks as the eighth most common cancer type in the United States among both sexes. Thyroid cancer most frequently affects middle-aged adults, with 60.4% of new cases diagnosed in patients younger than 55 years. The median age at diagnosis is 50 years. Thyroid cancer affects women disproportionately; among all races, the age-adjusted incidence of thyroid cancer was 20.0 per 100,000 women vs 6.7 per 100,000 men from 2008 to 2012.³

The incidence of thyroid cancer has increased in recent years. Thyroid cancer is the most rapidly increasing cancer diagnosis in the United States. Much of this increasing prevalence can be attributed to a higher rate of diagnosis of small papillary tumors, often referred to as papillary microcarcinomas.²

The 5-year relative survival rate for patients with thyroid cancer is high, at 97.9%. In 2016, there will be an estimated 1980 deaths related to thyroid cancer in the United States.³ The rate of death from thyroid cancer increases with age. Although most new thyroid cancer diagnoses are made in middle-aged adults, most deaths occur when the disease is diagnosed at an older age. The median age at death is 73 years.

Patients with thyroid cancer have a high survival rate primarily because most tumors are diagnosed in earlier stages of disease. Approximately 68% of patients are diagnosed with localized disease, which is confined

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Table 1. Description of Recurrence Risk Groups According to the 2009 ATA Guidelines^a

Recurrence Risk Group	Disease Characteristics
Low risk	<p>Patients with papillary thyroid cancer and all of the following characteristics:</p> <ul style="list-style-type: none"> • No local or distant metastases • All macroscopic tumor has been resected • No tumor invasion of locoregional tissues or structures • Tumor does not have aggressive histology • If RAI is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan • No vascular invasion • Clinical N0 or ≤ 5 pathologic N1 micrometastases (<0.2 cm in largest dimension) <p>Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer Intrathyroidal, well-differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including <i>BRAF</i>V600E–mutation (if known)</p>
Intermediate risk	<p>Microscopic invasion of tumor into the perithyroidal soft tissues RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan Aggressive histology Papillary thyroid cancer with vascular invasion Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension Multifocal papillary microcarcinoma with ETE and <i>BRAF</i>V600E–mutation (if known)</p>
High risk	<p>Macroscopic invasion of tumor into the perithyroidal soft tissues (gross extrathyroidal extension) Incomplete tumor resection Distant metastases Postoperative serum thyroglobulin suggestive of distant metastases Pathologic N1 with any metastatic lymph node ≥ 3 cm in largest dimension Follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion)</p>

ATA, American Thyroid Association; ETE, extrathyroidal extension; RAI, radioactive iodine.

^aWith proposed modification from the 2015 ATA guidelines.

Adapted from Haugen BR et al. *Thyroid*. 2016;26(1):1-133.⁵

to the primary tumor site. Another 26% of patients are diagnosed with regional spread (when the primary tumor has spread to regional lymph nodes). The 5-year relative survival rate for localized thyroid cancer is 99.9%, and decreases slightly to 97.8% for patients with regional spread. In contrast, the 5-year relative survival for patients with distant metastasis is 54.1%; however, just 4% of patients are diagnosed with this late stage of disease.³

Staging and Recurrence Risk in DTC

The American Joint Committee on Cancer (AJCC) TNM staging system can be used to describe thyroid cancers, but it was developed to predict the risk of death, not recurrence. Mortality from thyroid cancer is very low, and therefore the AJCC TNM system is not particularly useful in daily clinical practice. Instead, many clinicians use a 3-tiered staging system developed in 2009 by the American Thyroid Association (ATA) to determine the risk for recurrence, a more relevant outcome measure for DTC.⁴ This system uses clinicopathologic characteristics to classify DTCs as being

at low, intermediate, or high risk of recurrence. The 2015 updated guidelines from the ATA continue to recommend this risk stratification system, and include proposed modifications to the risk groups (Table 1).⁵ Low-risk patients make up approximately 60% of the patient population and have overall survival rates that approach 100%, with very low rates of recurrence (1% to 2%). Most patients in the intermediate-risk group also do well, with overall survival rates exceeding 95%. However, recurrence rates in this group can be as high as 20% to 30%. High-risk patients have overall survival rates of approximately 50%, and most patients have persistent disease despite treatment.

Traditional Treatment

Historically, DTC was treated with a one-size-fits-all approach, with nearly all patients undergoing surgical resection of the thyroid, followed by RAI treatment and intense follow-up. An improved understanding of patient prognosis and the risk of recurrence has led both the ATA and the National Comprehensive Cancer Network

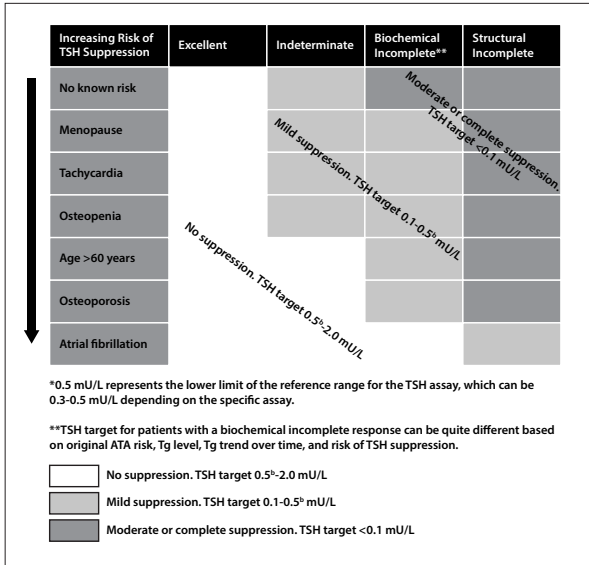


Figure 1. Thyrotropin targets for long-term thyroid hormone therapy. TSH, thyroid-stimulating hormone. Adapted from Haugen BR et al. *Thyroid*. 2016;26(1):1-133.⁵

(NCCN) to advocate a more tailored approach to treatment in their guidelines.^{1,4} Initial treatment decisions are made by balancing the risk of recurrence and estimated disease-specific mortality against the potential benefits and risks of the therapy under consideration.^{1,5} In most clinical practices, management of DTC is now based on a decision-making process shared between the patient and his or her physician.

Low-risk patients with papillary microcarcinomas are given the option to undergo observation or surgery, making active surveillance an important concept for these very small tumors. Patients with low-risk or intermediate-risk DTC may be appropriate candidates for an ipsilateral lobectomy (partial removal of the thyroid) as opposed to a total thyroidectomy. The extent of surgical resection is determined on an individualized basis, with most patients still undergoing a total thyroidectomy. Patients with high-risk DTC uniformly undergo a total thyroidectomy. Any involved lymph nodes are also removed at the time of surgery using a compartment-oriented neck dissection management approach.⁵

DTC tumors express the receptor for TSH and respond to TSH stimulation by increasing the rate of cell growth. Therefore, levothyroxine therapy is commonly employed to suppress TSH production in patients with DTC. Historically, TSH levels were suppressed to undetectable levels in all patients. According to the ATA guidelines, patients with high-risk DTC should have their TSH levels suppressed to below 0.1 mU/L. Patients with intermediate-risk DTC should have their TSH levels suppressed to between 0.1 and 0.5 mU/L. For low-risk patients who have undergone a lobectomy, it is recom-

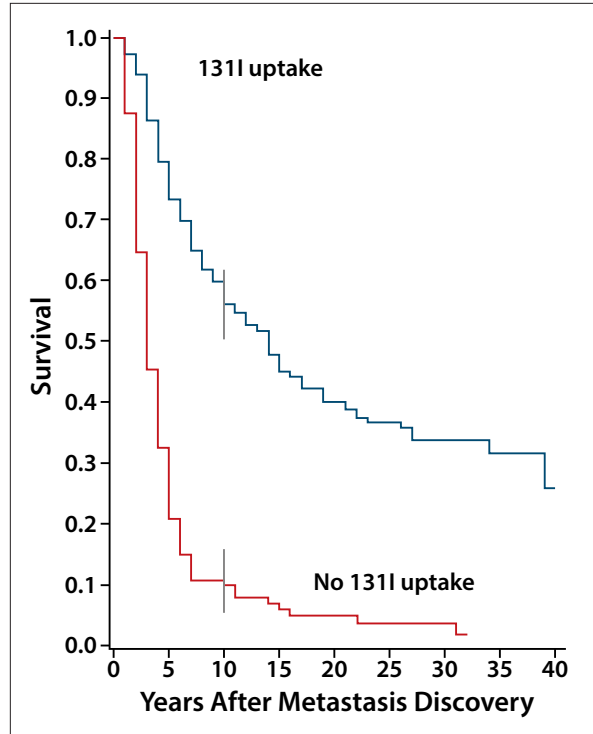


Figure 2. Patients with nonavid tumors are unlikely to benefit from treatment with radioactive iodine. Adapted from Durante C et al. *J Clin Endocrinol Metab*. 2006;91(8):2892-2899.⁶

mended that the TSH levels be maintained between 0.5 and 2 mU/L while surveillance for recurrence continues. For low-risk patients who have undergone remnant ablation, recommended TSH levels are dependent upon whether the patient has low-level serum thyroglobulin (TSH level of 0.5 to 2 mU/L) or undetectable serum thyroglobulin (TSH level of 0.1 to 0.5 mU/L).⁵ However, with increased knowledge of a patient's risk for recurrence and the risks associated with long-term TSH suppression, there has been a paradigm shift in the management of TSH levels (Figure 1).

A similar paradigm shift has occurred in the use of RAI adjuvant therapy. In the ATA guidelines, RAI treatment is not recommended for low-risk patients with papillary microcarcinomas. It is usually recommended in patients who have an aggressive histology or vascular invasion. Patients with tumors that are not avid are unlikely to benefit from treatment with RAI (Figure 2).⁶ Although RAI may be an option for patients with intermediate-risk tumors that are larger than 4 cm, the presence of other adverse features should be considered. For intermediate-risk patients with microscopic extrathyroidal extension, central compartment neck lymph node metastases, or lateral neck/mediastinal lymph node metastases, RAI treatment is generally favored because these patients have a higher risk for recurrent disease, but other factors, such as the number and

size of involved lymph nodes, the degree of extrathyroidal extension, and the specific histology, must be considered before making a final decision. RAI treatment is recommended for all high-risk DTC patients.⁵

Progressive Disease

Current first-line treatment of DTC, which consists of surgery and adjuvant RAI therapy, will cure the majority of patients with low-risk or intermediate-risk DTC. Even the small proportion of patients who do experience recurrent disease typically respond to subsequent surgery and RAI treatment. There remains, however, a small group of patients who continue to have persistent or recurrent disease despite traditional treatment. Most often, these patients are classified as having high-risk and/or advanced disease at presentation (stage III or IV). Metastases to the lung, the most common site of distant metastases, are usually multiple and not amenable to surgical cure in most cases.

DTC metastases, like the primary tumors, will often actively concentrate RAI. Therefore, RAI therapy should be considered even in the setting of progressive metastatic disease. Patients who are initially suspected to be refractory to RAI should be carefully assessed to ensure they have appropriate TSH levels and no contaminating normal iodine, which could negate the effects of RAI.

According to the ATA guidelines, RAI-refractory DTC is classified in 4 basic ways: (1) the malignant or metastatic tissue fails to ever concentrate RAI; (2) the tumor tissue loses the ability to concentrate RAI after previously showing evidence of RAI responsiveness; (3) RAI is concentrated in some but not all lesions; and (4) metastatic disease continues to progress despite a significant concentration of RAI. In general, disease progresses very slowly in patients with RAI-refractory DTC.⁵ It is not unusual for an RAI-refractory patient with pulmonary metastases to show only a millimeter of tumor growth every 1 to 2 years. Such patients can typically be observed for several years before more aggressive therapy is considered.

However, some patients with RAI-refractory progressive disease exhibit more rapid disease progression. Often, these patients have DTCs that are more poorly differentiated (such as Hürthle cell carcinomas). Characteristically, these tumors are more structurally significant (larger than 1 cm in diameter and positive on ¹⁸F-fluorodeoxyglucose positron emission tomography [FDG-PET] scans), and patients show a rapid serum thyroglobulin doubling time (<1-2 years). These patients should undergo routine cross-sectional imaging studies every 6 months (or more often). The aggressive nature of this disease suggests that it is likely to cause significant morbidity or mortality, and therefore these patients should be considered candidates for systemic therapy.

Considering Systemic Therapy

Decisions regarding the management of patients with RAI-refractory, rapidly progressing DTC are best made in the context of a multidisciplinary care team. In some cases, these patients may be candidates for localized palliative treatment of the distant metastasis (through either a metastasectomy, radiofrequency ablation, embolization, or external beam radiation). Endocrinologists, who are often the primary care physician for patients with DTC, may be less experienced with the management of these complicated cases and often benefit from the input of medical and surgical oncologists.

One of the more difficult decisions made in the care of patients with RAI-refractory, progressive DTC is when to initiate systemic therapy. Asymptomatic patients with subcentimeter pulmonary nodules that are either unchanging or slowly progressive (doubling every 5 years) can be safely considered for watchful waiting. Systemic therapy should be considered in patients who become symptomatic or who have lesions that are larger than a centimeter or that are progressing rapidly (doubling within 2 or 3 years). Again, this decision should be made in the context of a multidisciplinary care team. Ideally, an endocrinologist consults with an oncologist on a particular patient throughout the course of several months, sharing in the decision-making process on when to initiate systemic therapy.

Disclosure

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Sequencing of Tyrosine Kinase Inhibitors in Progressive Differentiated Thyroid Cancer

Marcia S. Brose, MD, PhD

Director, Center for Rare Cancers and Personalized Therapy

Abramson Cancer Center

Associate Professor

Department of Otorhinolaryngology, Head and Neck Surgery

Department of Medicine, Division of Hematology and Oncology

Perelman School of Medicine

University of Pennsylvania

Philadelphia, Pennsylvania

In the past decade, research has shown that the majority of patients with advanced DTC show significant aberrations in cell signaling. Most of these aberrations occur as the result of mutations in the tyrosine kinases and other molecules found in the pathways important for cell growth, including the RAF/MEK/ERK and the AKT/mTOR pathways. Both of these pathways are important for intracellular signaling. When activated, they result in increased cell growth and increased angiogenesis, and are therefore considered oncogenic.

Patients with advanced thyroid cancer exhibit mutations in these cell-signaling pathways. Often, the progression of disease from a more indolent tumor to a more aggressive cancer that is RAI-refractory coincides with the build-up of these mutations. The proportion of DTCs with mutations increases as the tumors become more poorly differentiated and more advanced. Additionally, many of the mutated proteins in these signaling pathways are kinase enzymes that can be inhibited with small-molecule kinase inhibitors. DTCs are highly vascular tumors, meaning that they are dependent on angiogenesis. Angiogenesis is mediated in part by the vascular endothelial growth factor (VEGF) receptor, and can therefore be disrupted by the use of kinase inhibitors that target (either in part or specifically) the VEGF receptor. It may be possible to inhibit DTC progression with a single kinase inhibitor that can target both BRAF and the VEGF receptor.

Tyrosine kinase inhibitors (TKIs) are targeted agents with this dual mechanism of inhibition. Many of these agents have varying potencies across different targets, including RAF, MEK, and the VEGF receptor. By inhibiting the VEGF receptor and disrupting angiogenesis, TKIs limit tumor growth by decreasing their blood supply. In addition, TKIs exert direct anticancer activity on the tumor cells by targeting signaling molecules within or upstream of the RAF/MEK/ERK pathway.

Approved TKIs in Thyroid Cancer

Two TKIs are approved by the US Food and Drug Administration (FDA) for patients with progressive DTC. Sorafenib and lenvatinib are indicated for the treatment of patients with locally recurrent or metastatic, progressive DTC that is refractory to RAI.^{1,2}

Sorafenib

Sorafenib is an oral, multitargeted kinase inhibitor of the VEGF receptors 1, 2, and 3; RET (including RET/PTC); RAF (including mutated *BRAF* V600E); and platelet-derived growth factor receptor β (PDGFR β). The approval of sorafenib for the treatment of progressive RAI-refractory DTC was based on results of the DECISION (Study of Sorafenib in Locally Advanced Metastatic Patients With Radioactive Iodine Refractory Thyroid Cancer) study.³ DECISION was a multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trial designed to assess the efficacy and safety of sorafenib in the treatment of RAI-refractory DTC. The study randomly assigned 419 patients in a 1:1 fashion to receive treatment with either sorafenib (400 mg twice daily) or placebo. All patients had locally advanced or metastatic RAI-refractory progressive DTC as assessed by investigator review. Additionally, all patients had an Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2; adequate bone marrow, liver, and renal function; and a serum TSH concentration of less than 0.5 mIU/L. Patients who had received prior treatment with either cytotoxic chemotherapy or a targeted therapy were excluded from the study. Multiple tumor histologies were permitted, but more than half of patients in each arm had papillary tumors. Crossover to the sorafenib arm was offered to patients in the placebo arm who developed disease progression.³

The primary endpoint of the DECISION study, progression-free survival, was met. Median progression-free survival was significantly improved among patients in the sorafenib arm vs the placebo arm (10.8 vs 5.8 months, hazard ratio [HR], 0.59; 95% CI, 0.45-0.76; $P < .0001$; Figure 3). This improvement corresponded to a 41% reduction in the risk of progression or death with sorafenib. The benefit in progression-free survival was observed across all prespecified patient subgroups, including age, sex, geographic region, tumor histology, lung or bone metastasis, ^{18}F -FDG uptake, and number and size of tumor lesions.³ A subanalysis of the DECISION trial presented at the 2014 American Thyroid Association meeting showed that sorafenib was associated with a significant clinical effect regardless of the existence of thyroid carcinoma symptoms at baseline (Figure 4).⁴

Overall survival, a secondary endpoint of the DECISION trial, did not significantly differ between the sorafenib and placebo arms (HR, 0.80; 95% CI, 0.54-1.19; $P = .14$). However, the crossover from the placebo arm (which occurred in 71.4% of placebo-treated patients) may have affected this result. Another secondary endpoint, objective response rate, was improved with sorafenib vs placebo (12.2% vs 0.5%; $P < .0001$). All of the responses were partial. The median duration of response in sorafenib-treated patients was 10.2 months.³

Most adverse events reported in the DECISION study were grade 1 or 2 in severity. Among sorafenib-treated patients, the most frequently reported adverse events included hand-foot skin reaction (76.3%), diarrhea (68.6%), alopecia (67.1%), rash or desquamation (50.2%), fatigue (49.8%), weight loss (46.9%), and hypertension (40.6%). Serious adverse events included secondary malignancy (4.3%), dyspnea (3.4%), and pleural effusion (2.9%). Among patients receiving sorafenib, adverse events led to dose interruptions in 66.2% and dose reductions in 64.3%. A total of 18.8% of patients discontinued treatment with sorafenib. Hand-foot skin reaction was the most frequent cause for dose interruptions and drug withdrawals.³

Lenvatinib

The second targeted agent to receive approval in RAI-refractory, progressive DTC was lenvatinib. This TKI is an oral, multitargeted inhibitor of the VEGF receptors 1, 2, and 3; fibroblast growth factor receptors (FGFR) 1 through 4; PDGFR α ; RET; and KIT. The safety and efficacy of lenvatinib in progressive DTC was established in the SELECT (Study of [E7080] Lenvatinib in Differentiated Cancer of the Thyroid) study, a randomized, double-blind, multicenter, phase 3 clinical trial.⁵

SELECT randomized a total of 329 patients in a 2:1 fashion to receive lenvatinib (24 mg/day) or placebo.

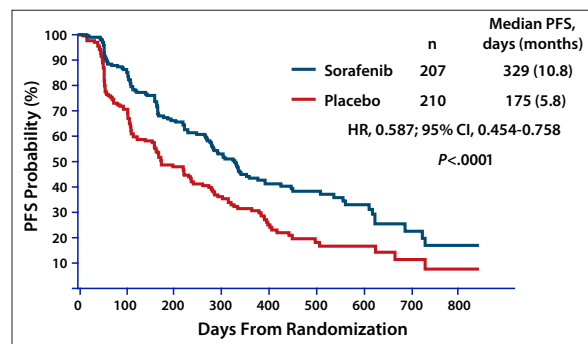


Figure 3. Median PFS in the phase 3 DECISION trial, which evaluated sorafenib in patients with locally advanced or metastatic radioactive iodine–refractory differentiated thyroid carcinoma. DECISION, Study of Sorafenib in Locally Advanced Metastatic Patients With Radioactive Iodine Refractory Thyroid Cancer; HR, hazard ratio; PFS, progression-free survival. Adapted from Brose MS et al. *Lancet*. 2014;384(9940):319-328.³

All patients had RAI-refractory DTC with evidence of progressive disease. Patients had an ECOG performance status between 0 and 2, and adequate bone marrow, renal, and liver function. Previous treatment with 1 prior VEGF-targeted therapy prior to enrollment was permitted, and reported in 25% of patients. Patients in the placebo arm who developed disease progression could crossover to receive lenvatinib.⁵

The primary endpoint of the SELECT study, median progression-free survival, was prolonged by approximately 15 months with lenvatinib vs placebo (18.3 months vs 3.6 months [HR 0.21; 99% CI, 0.14-0.31; $P < .001$]; Figure 5). The benefit in progression-free survival seen with lenvatinib was observed in all prespecified patient subgroups. Importantly, median progression-free survival was also significantly improved with lenvatinib compared with placebo even among patients who had previously received VEGF-targeted therapy (15.1 months vs 3.6 months), suggesting that lenvatinib has efficacy in the second-line setting.⁵

Median overall survival had not been reached in either treatment arm at the time of data analysis. The objective response rate among lenvatinib-treated patients was 65%. Four patients achieved a complete response. Durable stable disease (23 weeks or longer) was seen in an additional 15.3% of patients.⁵

The most common treatment-related adverse events of any grade in the lenvatinib arm were hypertension (67.8%), diarrhea (59.4%), fatigue or asthenia (59.0%), decreased appetite (50.2%), decreased weight (46.4%), and nausea (41.0%). A total of 14.2% of lenvatinib-treated patients discontinued the study drug owing to adverse events. In the lenvatinib group, 6 of 20 deaths that occurred during the treatment period were considered by the investigators to be drug-related.⁵

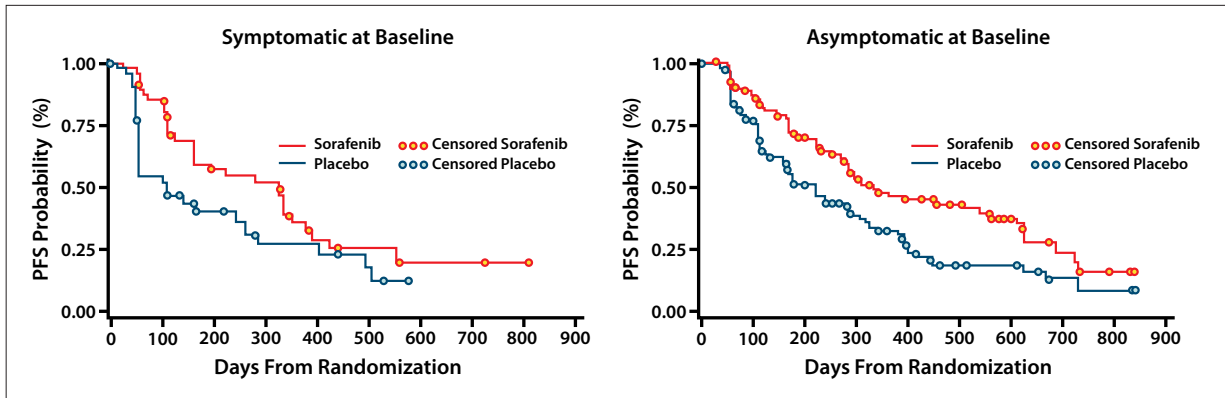


Figure 4. A subanalysis of the DECISION trial assessing PFS according to the presence of symptoms at baseline. DECISION, Study of Sorafenib in Locally Advanced Metastatic Patients With Radioactive Iodine Refractory Thyroid Cancer; HR, hazard ratio; PFS, progression-free survival. Adapted from Schlumberger M et al. ATA abstract 13. *Thyroid*. 2014;24(suppl 1).⁴

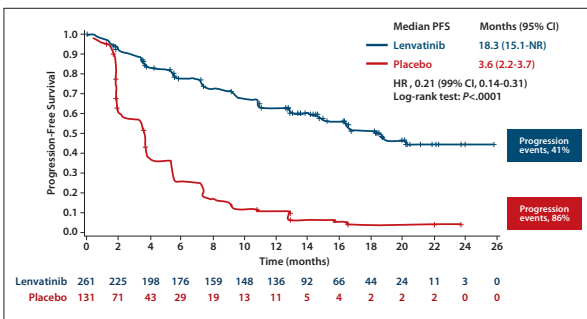


Figure 5. Median PFS in the phase 3 SELECT trial, which evaluated lenvatinib in patients with radioactive iodine–refractory differentiated thyroid carcinoma. HR, hazard ratio; NR, not reached; PFS, progression-free survival; SELECT, Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid. Adapted from Schlumberger M et al. *N Engl J Med*. 2015;372(7):621-630.⁵

Considerations in the Interpretation of the Trial Results

It is notable that the patients in the placebo arm of the SELECT study had a median progression-free survival of just 3.6 months, compared with 5.8 months among the placebo-treated patients in the DECISION trial. This difference suggests that the patients in the SELECT study had more actively progressing disease at study entry, which might be attributed to 2 reasons. First, in the DECISION trial, progressive disease was determined by the investigator prior to study entry. In contrast, the SELECT trial relied on central review, a potentially more rigorous process. Second, the SELECT study used the updated version of the Response Evaluation Criteria In Solid Tumors (RECIST), whereas the DECISION study used the older, less rigorous criteria.

Another significant difference between the DECISION and SELECT trials was that SELECT permitted enrollment of patients who had previously received a VEGF receptor-targeted agent. (In most cases, this agent was sorafenib.) The median progression-free survival among previously treated

patients was 15.1 months. Although this outcome was shorter than the 18.2 months achieved by treatment-naïve patients, it is still markedly prolonged compared with the 3.6 months seen in the placebo arm. These data suggest that lenvatinib remains highly active even in the second-line setting. Some clinicians have been reassured to know that there is an effective option for patients who progress on first-line sorafenib. Currently, there are no comparative study data available for the use of sorafenib after first-line lenvatinib.

The response rate reported with sorafenib in the DECISION trial (12.2%) was relatively modest, especially considering that all of the responses were partial. When patients with stable disease (for at least 6 months) were included, the clinical benefit rate reached 54.1%, which was significantly greater than the 33.8% reached in the placebo arm ($P<.0001$). The response rate with lenvatinib in the SELECT study was high, at 65%. Most of the responses were partial, but 4 were complete. Therefore, both sorafenib and lenvatinib achieve a high rate of response or stabilized disease.

Many clinicians believe that the median progression-free survival achieved with sorafenib in the DECISION study is a low estimate of the actual efficacy of the drug. Many of the sites that participated in the DECISION study were administering this targeted agent for the first time. There is the possibility that these investigators were more prone to manage adverse events by reducing the dosage of sorafenib.

These considerations are important and also serve to explain why the results of the DECISION and SELECT studies cannot be compared. Likewise, until sorafenib and lenvatinib are evaluated in a head-to-head study, they cannot be directly compared.

Sequencing TKIs

Most patients with RAI-refractory, progressive DTC will ultimately receive treatment with both sorafenib and lenvatinib, regardless of which therapy is started first.

Because of the differences between the DECISION and SELECT trials, and because the appropriate clinical studies have not yet been performed, the sequence in which these agents should be administered is not yet clear.

There are patient subgroups for which some additional information is known. For example, in the DECISION trial, the response to sorafenib was often less strong among patients whose largest lesion was less than 1.5 cm. Therefore, for these patients, active surveillance is the best approach until the largest lesion progresses to more than 1.5 cm (unless symptomatic disease or another reason prompts earlier treatment). In contrast, given the high activity shown in the SELECT patient population, clinicians may consider lenvatinib as first-line therapy in patients with very actively aggressive disease, with fast doubling times, and also in patients who are symptomatic and who would benefit from a change in the trajectory of the disease.

The DECISION trial and the SELECT trial included subgroup analyses based on the presence of *BRAF* or *RAS* mutations. The presence of these mutations did not impact response to sorafenib or lenvatinib. Therefore, molecular genetic analysis for *BRAF* and *RAS* should not be used to select patients for treatment with these therapies.

Patients with *RAS* mutations are more likely to be poorly differentiated. In the SELECT trial, an analysis of patients with both poorly differentiated and *RAS*-mutated disease showed that they were still likely to achieve a statistically significant benefit with sorafenib, but they are also more likely to progress rapidly. Although these patients will initially benefit from sorafenib, they may need to quickly progress to second-line therapy. In contrast, patients with better papillary histology may not need additional therapy for 2 or even 3 years.

A preplanned analysis was performed in the SELECT study based on patient age. Patients ages 65 years or younger were compared with those older than 65 years. The younger patient group had a benefit in progression-free survival, but not in overall survival. The older patient group showed a statistically significant benefit for both endpoints. This analysis was the first to show an overall survival difference according to patient age in DTC, and the findings suggest that patients older than 65 years should be treated with lenvatinib. The disproportionate benefit in overall survival observed with lenvatinib in older patients may be because this patient group is more likely to succumb to their disease. In many instances, physicians are more likely to withhold a drug in older patients; however, these results suggest that the opposite should occur in this case. In fact, older age may be a reason to select lenvatinib as the first-line therapy.

In clinical practice, we use both sorafenib and lenvatinib in the first-line setting. Treatment is personalized to the patient and his or her disease.

When to Consider a TKI

At my institution, our decision to consider systemic therapy in patients with RAI-refractory, progressive DTC is based on a slightly different criteria from that described by Dr Tuttle in the previous article. Systemic therapy is considered in any patient with DTC who has progressive disease that is no longer amenable to treatment with RAI. This can mean that the tumor tissue is no longer RAI-avid, the tumor is continuing to progress despite a recent dose of RAI, or the disease progresses even after administration of high doses of RAI.

There is some discussion regarding the amount of tumor burden that should initiate systemic therapy. Instead of abiding by a defined rule, the clinician should consider 3 factors: the location of the disease, the size of the disease, and the rate of disease progression. These factors are usually best evaluated by the clinician who will ultimately be the treating physician. Therefore, once the patient is no longer amenable to RAI, regardless of how fast the disease is progressing or how much tumor burden they have, they should be seen by a medical oncologist with experience in treating advanced thyroid cancer. The oncologist should assess the burden of disease and the rate of disease progression to determine when systemic therapy would best be started. If the patient has relatively indolent disease with a low tumor burden and is asymptomatic, the oncologist may initially recommend an active surveillance approach for the patient. Active surveillance involves imaging studies performed every 3 to 6 months. If disease progression seems to increase in pace, or if symptoms arise, the patient may be considered a candidate for targeted therapy.

Some evidence from the DECISION and SELECT trials has suggested that patients with a lower tumor burden (largest lesion <1.5 cm) may derive less benefit from sorafenib but not lenvatinib. If a patient's largest lesion is less than 1.5 cm, another negative factor may need to be present in order to justify initiation of targeted therapy. Such factors can include a large tumor burden (ie, multiple lesions), symptomatic disease, or pleural-based lesions that are more likely to cause a pleural effusion.

The oncologist may also instruct the patient to begin preventive measures (including both pharmacologic and nonpharmacologic interventions) that can minimize adverse reactions to systemic therapy. These measures may include nutrition optimization and interventions focused on improving strength and muscle balance.

Adverse Events Associated With TKIs

Adverse events with sorafenib and lenvatinib in the clinical trials mirrored what is experienced in clinical practice. One of the primary adverse events experienced by patients with

sorafenib is hand-foot skin reaction. Hypertension may also occur. Additionally, some patients experience late diarrhea. For lenvatinib, the top adverse events in clinical practice are hypertension, proteinuria, diarrhea, and weight loss.

The adverse events are manageable, but they must be addressed by a clinician who is experienced with TKIs and who can anticipate their development. It is important to manage adverse events aggressively with medications, including over-the-counter therapies. This approach will help to prevent the need for significant and prolonged dose reductions, which will likely impact the efficacy of the drug. For example, hand-foot skin reaction can often be kept to grade 1 or a tolerable grade 2 with prophylactic therapy, including ibuprofen to help mitigate the pain. Additionally, brief drug holidays can be used to mitigate hand-foot skin reaction. Just a few dose holidays or dose reductions may enable a patient to subsequently tolerate the higher recommended dose.

In some cases, adverse events may help the clinician select which TKI to use as first-line therapy for a particular patient. However, since all patients with RAI-refractory progressive DTC should receive treatment with both agents, they will have to face both side effect profiles.

Some clinicians consider starting with a lower dosage of the TKI that is increased according to the patient's tolerance. I strongly caution against this approach because in most cases, it will prevent the patient from reaching the same high efficacious dose that would have been reached if the dose had been started high and then reduced. As a result, the same level of efficacy may not be reached. In my practice, we administer these agents in the same way they were given in the clinical trials in order to achieve the same clinical benefit.

Potential for Combination Therapy

Several combination regimens have already been investigated in patients with RAI-refractory, progressive DTC. One such combination is sorafenib or lenvatinib plus the mTOR inhibitor everolimus. The rationale for this combination was based on preclinical data showing that patients at the time of progression had increased activity in the AKT/MTOR pathway, as well as positive feedback in the RAF/MEK/ERK pathway.⁶ In addition, patients with lower levels of activated AKT are more likely to obtain a response to sorafenib.⁷

In a phase 2 study of patients who had progressed on sorafenib, everolimus was added to sorafenib therapy. Patients treated with this combination showed a median progression-free survival of 13.9 months (Figure 6).⁸ Interestingly, the sorafenib-plus-everolimus combination was found to be more tolerable when these therapies were given sequentially (sorafenib followed by everolimus) than when started together. A similar clinical trial is being initiated in which everolimus will be evaluated in combination with lenvatinib.⁹

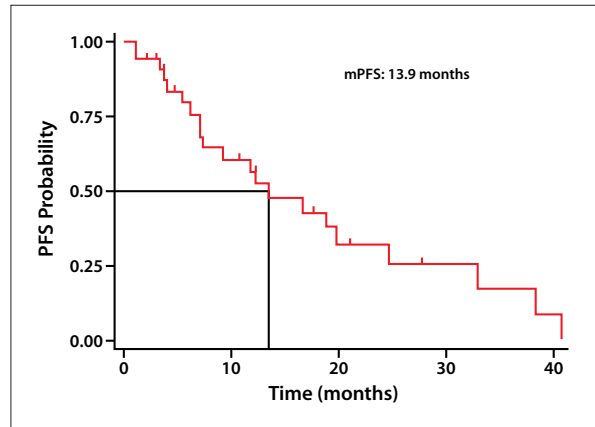


Figure 6. PFS in a phase 2 study of everolimus plus sorafenib in patients with metastatic differentiated thyroid cancer who had progressed on sorafenib. m, median; PFS, progression-free survival. Adapted from Brose MS et al. ASCO Abstract 6072.⁸

It is not yet recommended that the sorafenib-plus-everolimus combination be used as first-line treatment. These TKIs are highly effective as single agents, and there are not yet enough data to support the increased risk of adverse events that occurs when they are given concurrently. In countries where lenvatinib is not yet available, the sorafenib-plus-everolimus combination strategy is now being used fairly regularly as a second-line approach.

Ultimately, long-term results rely on the expertise of the physician in sequencing the therapies and managing adverse events. It is especially important to maximize the doses that the patients can tolerate.

Areas of Research

There are additional targeted therapies under investigation for patients with RAI-refractory progressive DTC. Single-agent therapies, especially those directed at mutations, are generating a great deal of interest in this patient population. An example would be the agents that target the *BRAF* V600E-mutated protein. The *BRAF* V600E mutation is found in 60% of papillary DTCs, and causes an overactivation of the RAF/MEK/ERK signaling pathway. There are now 2 kinase inhibitors, dabrafenib and vemurafenib, that directly target cells with this mutation. Ultimately, these other targeted agents will likely augment our current treatments.

A phase 2 study evaluated vemurafenib in a molecularly targeted subset of 51 patients with *BRAF* V600E-mutated papillary DTC. The best overall response rate was 26% in those who had received previous TKI therapy and 35% in those who were TKI-naive.¹⁰

There is a phase 1 trial of cabozantinib, which is currently approved for the treatment of medullary thyroid cancer.¹¹ Early clinical data suggest that this agent is also extremely active in DTC. We have found anecdotally that even heavily

pretreated patients (those who have received both sorafenib and lenvatinib, and even additional targeted agents [given in clinical trials]) still show a response to cabozantinib, suggesting that this agent may be active in this setting.

Another area of research involves immunotherapy. An ongoing clinical trial is evaluating the combination of lenvatinib with the PD-1–targeted immunotherapy pembrolizumab. Additional research is evaluating the appropriate doses. High levels of grade 3 hypertension led most patients to require a reduced dose of lenvatinib in the first 3 months of the clinical trial. There are now additional studies underway to determine whether lower initial doses of lenvatinib could be equally effective but cause fewer adverse events.

Disclosure

Dr Brose is a consultant or advisor to Bayer and Onyx. She has received honoraria and research funding from Bayer.

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Best Use of the Tyrosine Kinase Inhibitors in Progressive Differentiated Thyroid Cancer: Discussion

R. Michael Tuttle, MD, and Marcia S. Brose, MD, PhD

H&O What approach would you take in a patient receiving systemic therapy with good disease control who shows tumor growth at just 1 metastatic site, such as a bone or lymph node metastasis?

R. Michael Tuttle, MD Our approach would be to continue the systemic therapy but to use a localized therapy for that one lesion that is progressing. For example, we may have a patient on a tyrosine kinase inhibitor who shows stable disease with the exception of one bone lesion that begins to grow. We would radiate that bone metastasis and continue the tyrosine kinase inhibitor therapy.

Marcia S. Brose, MD, PhD When patients receiving sorafenib or lenvatinib progress in a single lesion, we usually administer external beam radiation. In these cases, the TKI can be continued. In some cases, you can get another whole year of disease control without switching therapies.

H&O What is the potential for the use of redifferentiation agents to resensitize RAI-refractory patients?

R. Michael Tuttle, MD Several trials have investigated strategies to “redifferentiate” metastatic RAI-refractory

DTC, rendering them once again sensitive to RAI. Pre-clinical studies suggest that inhibition of BRAF causes tumor xenografts to regain the ability to trap RAI.¹ This observation led to a pilot study in which patients with RAI-refractory progressive DTC were treated with selumetinib, a MEK1/2 inhibitor, for 4 weeks.² Selumetinib increased the uptake of RAI in 12 of 20 evaluable patients. The dosimetry threshold for RAI therapy was reached in 8 of these 12 patients; of these, 5 had confirmed partial responses and 3 had stable disease (Figure 7). The same concept is currently being tested in ongoing clinical trials, with a focus on identifying the best candidates for re-sensitization. For example, the phase 3 ASTRA (Adjuvant Selumetinib for Differentiated Thyroid Cancer, Remission After RAI) study is evaluating the complete remission rate following a 5-week course of selumetinib vs placebo.³

H&O What is the role of molecular testing in the treatment of patients with RAI-refractory progressive DTC?

R. Michael Tuttle, MD Many centers now can test tumor specimens for abnormalities in hundreds of genes. At Memorial Sloan Kettering Cancer Center, we can test for aberrations in approximately 400 different genes. This strategy, known as deep gene sequencing, can help to determine if the tumor specimen contains a genetic aberration that can be rationally targeted with a targeted therapy such as a tyrosine kinase inhibitor. Most of us think that knowing the molecular profile of a tumor specimen can help guide more rational treatment decisions.

H&O Do you have additional advice on managing TKI-related adverse events?

Marcia S. Brose, MD, PhD For all TKIs, one important means to mitigate adverse events is to improve muscle mass. We tell patients to go to the gym and do weight lifting and strengthening (not aerobic) exercises. Part of the weight loss and fatigue that can occur with both sorafenib and lenvatinib is likely related to loss of muscle mass. I also work with the patient to create a nutritious, high-protein diet.

We brought together several physicians who prescribe sorafenib in several settings to talk specifically about these adverse events. Their recommendations were published in an article in *Seminars in Oncology*.⁴ Each adverse event is discussed in a separate section, and specific considerations for patients with thyroid cancer are

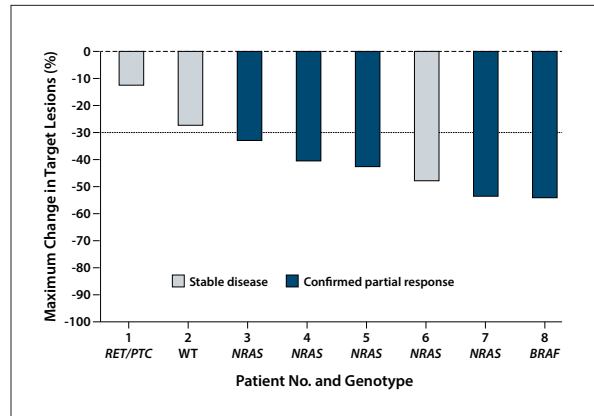


Figure 7. The maximum change in target lesions, relative to baseline, among patients who received therapeutic radioiodine in a study of the MEK 1/2 inhibitor selumetinib. WT, wild-type. Adapted from Ho AL et al. *N Engl J Med.* 2013;368(7):623-632.²

included. The sorafenib-related adverse events included in this discussion are hand-foot skin reaction, rash, upper and lower gastrointestinal distress (with a special focus on diarrhea), fatigue, and hypertension. Most of these adverse events range from grade 1 to 3 in severity. Additionally, most of the events generally present early in the course of sorafenib treatment. Management of these sorafenib-related adverse events focus on prevention and treatment to minimize their effects. Ultimately, the goal is to allow patients to remain on the recommended efficacious dose while maintaining or improving their quality of life.

Disclosure

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Slide Library

Differentiated Thyroid Cancers (DTCs)

- Arise from thyroid follicular cells and include papillary, follicular, and Hürthle cell thyroid cancers
- Papillary carcinoma accounts for 80% of thyroid cancers, whereas follicular carcinoma and Hürthle cell carcinoma account for 10% and 3% of thyroid cancers, respectively
- Papillary carcinomas are usually slow-growing thyroid cancers and have the best prognosis among the DTCs
- The prognosis for patients with follicular or Hürthle cell carcinoma is also very good in most cases

DTC, differentiated thyroid cancer.

Progressive Disease

- Current first-line treatment of DTC, which consists of surgery and adjuvant RAI therapy, will cure the majority of patients with low-risk or intermediate-risk DTC. Even the small proportion of patients who do experience recurrent disease typically respond to subsequent surgery and RAI treatment
- There remains a small group of patients who continue to have persistent or recurrent disease despite traditional treatment
- Most often, these patients are classified as having high-risk and/or advanced disease at presentation (stage III or IV). Metastases to the lung, the most common site of distant metastases, are usually multiple and not amenable to surgical cure in most cases

RAI-Refractory DTC

Definitions From the ATA

- The malignant or metastatic tissue fails to ever concentrate RAI
- The tumor tissue loses the ability to concentrate RAI after previously showing evidence of RAI responsiveness
- RAI is concentrated in some but not all lesions
- Metastatic disease continues to progress despite a significant concentration of RAI

ATA, American Thyroid Association.

Aberrations in Cell Signaling

- Most patients with advanced DTC show significant aberrations in cell signaling
- Most of these aberrations occur as the result of mutations in the tyrosine kinases and other molecules found in the pathways important for cell growth, including the RAF/MEK/ERK and the AKT/mTOR pathways
- The RAF/MEK/ERK and the AKT/mTOR pathways are important for intracellular signaling. When activated, they result in increased cell growth and increased angiogenesis, and are therefore considered oncogenic

TKIs in DTC

- Most patients with advanced DTC show significant aberrations in cell signaling
- TKIs can target both BRAF and the VEGF receptor
- Many of these agents have varying potencies across different targets, including RAF, MEK, and the VEGF receptor
- By inhibiting the VEGF receptor and disrupting angiogenesis, TKIs limit tumor growth by decreasing their blood supply
- TKIs exert direct anticancer activity on the tumor cells by targeting signaling molecules within or upstream of the RAF/MEK/ERK pathway

TKIs, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor.

TKIs in DTC: Sorafenib

- An oral multitargeted kinase inhibitor of the VEGF receptors 1, 2, and 3; RET (including RET/PTC); RAF (including mutated BRAF V600E); and platelet-derived growth factor receptor β (PDGFR β)
- Approved based on the DECISION trial, which showed improved PFS

DECISION, Study of Sorafenib in Locally Advanced Metastatic Patients With Radioactive Iodine Refractory Thyroid Cancer; PFS, progression-free survival.

TKIs in DTC: Lenvatinib

- An oral, multitargeted inhibitor of the VEGF receptors 1, 2, and 3; fibroblast growth factor receptors (FGFR) 1 through 4; PDGFR α ; RET; and KIT
- Approved based on the SELECT trial, which showed improved PFS

SELECT. Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid.

Potential for Combination Therapy

- Several combination regimens have been investigated in patients with RAI-refractory, progressive DTC
- In a phase 2 study of patients who had progressed on sorafenib, everolimus was added to sorafenib therapy. Patients treated with this combination showed a median progression-free survival of 13.9 months¹
- The sorafenib-plus-everolimus combination was more tolerable when these therapies were given sequentially (sorafenib followed by everolimus) than when started together

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Adverse Events Associated With TKIs

- Sorafenib
 - Hand-foot skin reaction
 - Hypertension
 - Diarrhea
- Lenvatinib
 - Hypertension
 - Proteinuria
 - Diarrhea
 - Weight loss

Management of Adverse Events Associated With TKIs

- The adverse events are manageable, but they must be addressed by a clinician who is experienced with TKIs
- It is important to manage adverse events aggressively with medications, including over-the-counter therapies
- Hand-foot skin reaction can often be kept to grade 1 or a tolerable grade 2 with prophylactic therapy, including ibuprofen to help mitigate the pain. Brief drug holidays can also be used
- An important way to mitigate adverse events is to improve muscle mass. Patients should go to the gym and perform weight lifting and strengthening (not aerobic) exercises
- Patients should follow a nutritious, high-protein diet

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