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New Frontiers and Treatment Paradigms for Thyroid Carcinoma

A Review of an Adjunct Symposium of the 2014 American Society of Clinical Oncology Annual Meeting

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Target Audience

This activity has been designed to meet the educational needs of physicians, nurses, academicians, researchers, investigators, support staff, and program directors from the field of oncology involved in the care of patients with thyroid carcinoma.

Statement of Need/Program Overview

Although mortality from thyroid cancer has remained relatively low, the proportion of patients dying of the disease is increasing. The pathologic and clinical differences observed across the spectrum of thyroid cancers influence the treatment approach. Risk group stratification is the most important clinical parameter for predicting prognosis and for planning treatment. Thyroid cancer is primarily managed with surgery, but there are cases in which surgery fails or is insufficient. Radioactive iodine (RAI) was established as a standard treatment more than 50 years ago. Soon after, it was recognized that RAI is not effective in all patients. Until recently, there were few options for patients with RAI-refractory disease. The elucidation of key signaling pathways in thyroid cancer has led to the development of targeted therapies that provide needed therapeutic options for these patients. In the past 4 years, the US Food and Drug Administration has approved 3 new treatments, and several other novel agents are in late-phase clinical trials.

Educational Objectives

After completing this activity, the participant should be better able to:

- Identify thyroid cancer patients who are refractory to radioactive iodine
- Employ risk group stratification to predict prognosis and plan treatment
- Describe the clinical significance of molecular pathways targeted by multikinase inhibitors
- Evaluate the latest clinical trial data supporting the use of tyrosine-kinase inhibitors in iodine-refractory thyroid carcinoma
- Apply strategies to manage the adverse events associated with novel targeted therapies for thyroid carcinoma

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This monograph was authored by an independent medical writer, Mindy Tanzola, PhD, based on presentations given at "New Frontiers and Treatment Paradigms for Thyroid Carcinoma," an adjunct symposium of the 2014 American Society of Clinical Oncology Annual Meeting, held on June 2, 2014.

Overview of Radioactive Iodine-Resistant Differentiated Thyroid Cancer

Steven I. Sherman, MD

In 2014, an estimated 62,980 individuals, predominately women, will be diagnosed with thyroid carcinoma.[1] From 2006 to 2010, the incidence of thyroid cancer increased at an annual rate of 5.4% in men and 6.5% in women.[1] Mortality from thyroid cancer has remained relatively low, at less than 5%, but the proportion of patients dying from the disease increased by approximately 13% from 2001 to 2010.[2] The trend toward increased mortality contrasts with that reported in other cancers, such as prostate cancer, colon cancer, and lung cancer in men, for which mortality rates declined by 40%, 33%, and 28%, respectively, throughout the same time.[2] Although overdiagnosis of microcarcinomas or minimal, low-risk disease may account for some of the increased incidence, there is clearly a subset of thyroid cancer patients who have a poor prognosis and lack effective therapy.

In general, the initial treatment for thyroid cancer is surgical (Figure 1). The best approach for most patients with tumors at least 1 cm in diameter is total thyroidectomy. The optimal approach for smaller tumors and the role of surgery for patients with microcarcinomas remain under debate.

There are several systemic approaches. The follicular cells from which differentiated thyroid cancer (DTC) originates are responsive to thyroid-stimulating hormone (TSH) via binding to the TSH receptor. Signaling through the TSH receptor induces thyroid hormone production and stimulates the differentiation and proliferation of thyroid cells. Nearly 80 years ago, it was recognized that treatment of metastatic thyroid cancer with thyroid extract results in shrinkage of pulmonary metastases.[3] It is now understood that in most cases, high doses of thyroid hormone are required to suppress TSH. However, the extent of TSH suppression required to attain a survival benefit in patients with metastatic thyroid cancer has been a subject of debate.

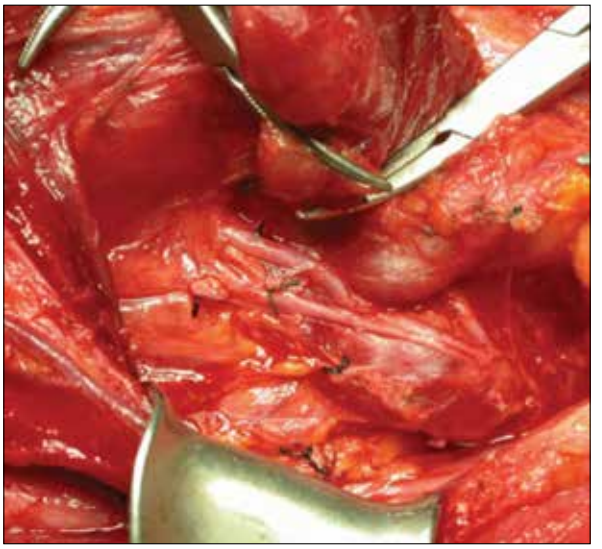

Figure 1. In general, the initial treatment for thyroid cancer is surgical. Total thyroidectomy is optimal for most patients with tumors that are at least 1 cm in diameter.

The unique ability of thyroid follicular cells to incorporate and organify iodine has been exploited for therapeutic use for many years (Figure 2). The potential therapeutic use of radioactive iodine (RAI) was first described in the medical literature in 1946,[4] and a report on the clinical efficacy of this approach was published in *LIFE Magazine* 3 years later.[5] RAI was subsequently established as a standard treatment for thyroid cancer. How-

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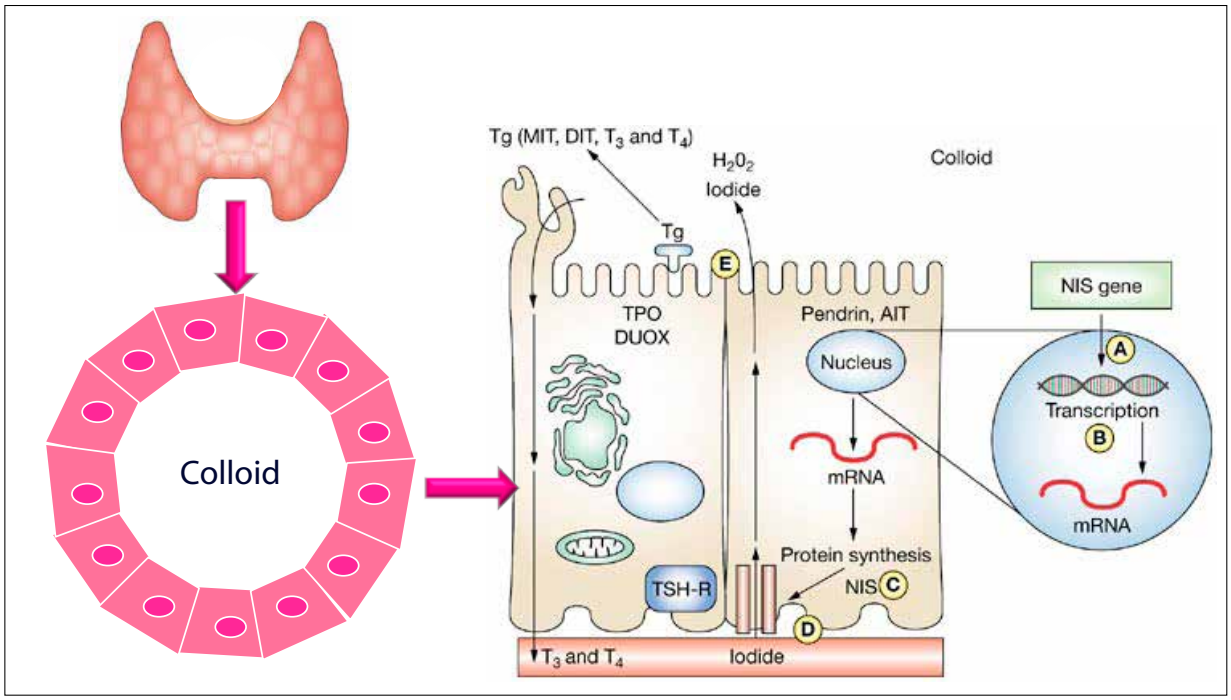

Figure 2. Iodine metabolism in the thyroid follicular cell. AIT, apical iodine transporter; DIT, diiodotyrosine; DUOX, dual oxidase; MIT, monoiodotyrosine; NIS, sodium-iodide symporter; Tg, thyroglobulin; TPO, thyroid peroxidase; TSH-R, TSH receptor; mRNA, messenger RNA. Adapted from Schlumberger M et al. *Nat Clin Pract Endocrinol Metab*. 2007;3(3):260-269.[9]

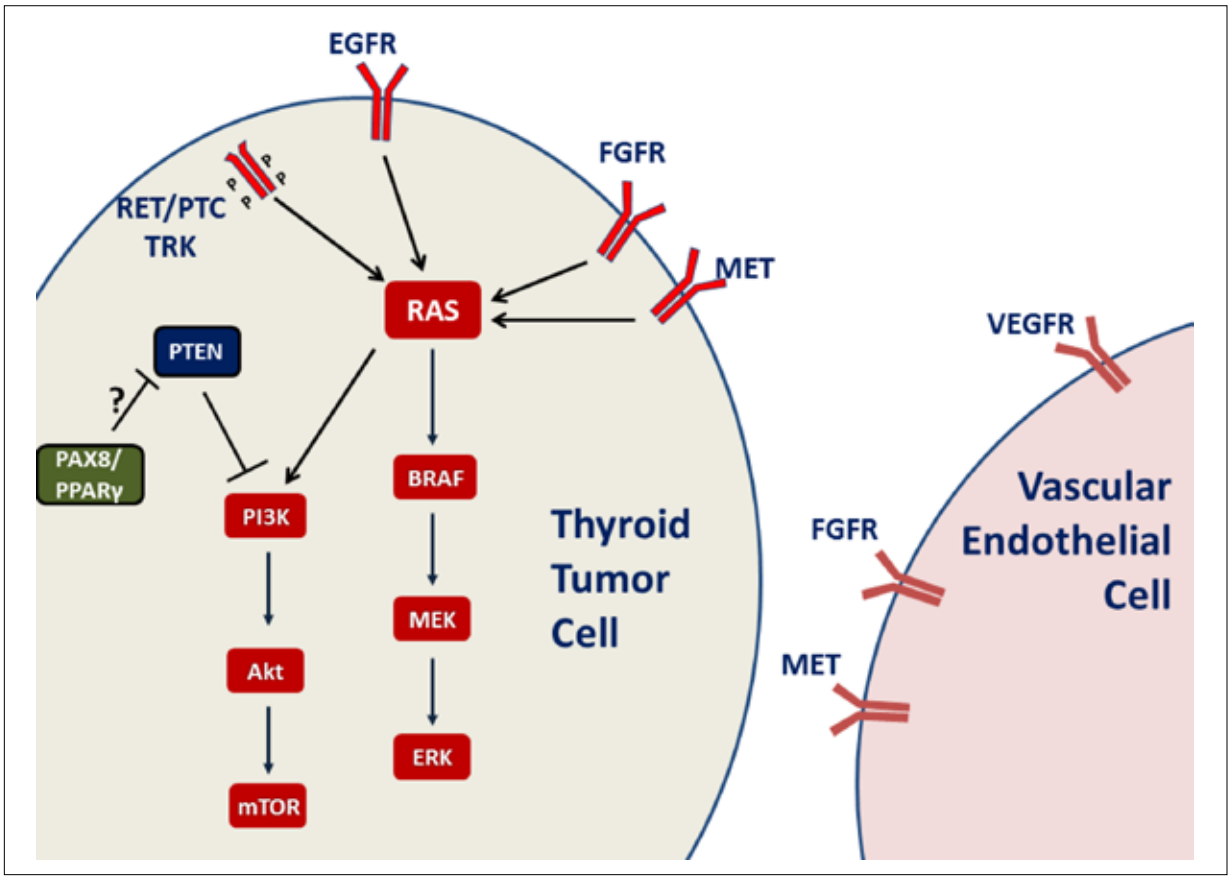

Figure 3. Key signaling pathways in thyroid cancer. FGFR, fibroblast growth factor receptor; VEGF, vascular endothelial growth factor receptor.

ever, it was soon recognized that RAI is not effective in all patients. In 1953, loss of iodine avidity was identified as an explanation for poor efficacy.[6] More than 60 years later, the mechanism of iodine avidity loss, and methods to reverse this process, remain under study.

Defining RAI-Refractory Disease

Several longitudinal studies have shown that in patients with thyroid cancer treated with RAI, lack of RAI uptake is significantly associated with poor survival.[7,8] As more is understood about the use of RAI in thyroid cancer, the definition of RAI-refractory disease is evolving. The clearest type of evidence is a lesion that is not RAI-avid on nuclear imaging. However, lesions that grow, or do not shrink, after 6 to 12 months of RAI therapy despite showing RAI uptake may also be considered RAI-refractory.

Historically, lack of response to RAI was addressed by increasing the dose of RAI, and therefore cumulative treatment with at least 600 mCi was included as a criterion for RAI refractoriness. It is now recognized, however, that cumulative treatment of 600 mCi or higher does not provide a survival advantage, and therefore this approach is no longer an appropriate standard of care.

The American Thyroid Association treatment guidelines are currently being updated, and are expected to include changes to the definition of RAI-refractory disease. Importantly, it is anticipated that the forthcoming guidelines will state that when a patient with DTC is considered to be RAI-refractory, there is no indication for further RAI treatment.

Until recently, there were few options for patients with RAI-refractory disease. In recent years, however, the elucidation of key signaling pathways in thyroid cancer has led to the development of targeted therapies that provide needed therapeutic options for these patients (Figure 3).

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Role of Surgical Therapy for Thyroid Cancer

Jatin P. Shah, MD, FACS

Thyroid cancer is primarily managed with surgery, but there are cases in which surgery fails or is insufficient. The prognosis for patients with thyroid cancer is strongly influenced by the extent of morphologic progression. In the approximately 80% of cases that develop from the follicular cell and differentiate as papillary or follicular carcinoma, the prognosis is typically excellent.[1] In the 10% to 15% of patients who present with a more aggressive histologic variant, such as tall cell or insular carcinoma, the prognosis is poor.[1] As the cancer becomes less well differentiated, the prognosis worsens. The worst outcomes are observed in the small minority of patients (<2%) who develop anaplastic carcinoma, which is rarely curable.[1]

Thyroid cancer subtypes vary in morphology and clinical features. Poorly differentiated tumors are typically larger, are associated with gross extrathyroid extensions, result in distant metastases, and are more likely to cause death. These poorly differentiated tumors are less likely to be diagnosed on a radioiodine scan and, therefore, are less likely to respond to RAI treatment. Because of their enhanced glucose metabolism and increased cell division, these types of tumors are more likely to be detectable by PET scan. Thus, the degree of iodine avidity and PET positivity are diametrically opposed in the biology of thyroid carcinoma.

Risk Stratification in Thyroid Cancer

The pathologic and clinical differences observed across the spectrum of thyroid cancers influence the treatment approach. Well-differentiated tumors are nearly always curable. In contrast, poorly differentiated tumors require aggressive surgery and adjuvant therapy (Figure 4); patients may require alternative treatment approaches if surgery or RAI therapy is no longer beneficial.

Within the subset of differentiated thyroid cancer, multiple factors have been identified that are associated with prognosis. One important factor is patient age (Figure 5). Among patients younger than 40 years, deaths from thyroid cancer are rare; the likelihood of cancer-related mortality increases with age.[2] The extent to which age affects prognosis is unique to thyroid cancer. Based on this increased mortality risk, older patients are more likely to require aggressive treatment, possibly including adjuvant therapy in addition to surgery.

Other factors associated with prognosis include age, sex, tumor size, presence of extrathyroid extensions, histologic grade, and the presence of distant metastases.[2] In general, factors associated with a low mortality risk include younger age (<45 years), small tumor size (<4 cm in diameter), lack of extrathyroid extension, well-differentiated histology, and no distant metastases. These characteristics apply to the majority of patients with papillary carcinoma. On the other end of the spectrum are high-risk patients—typically, older men with tumors larger than 4 cm, potentially with extrathyroid extension and often with distant metastases, who have poorly differentiated histology. In between these extremes is a group of patients with intermediate-risk disease; they include older patients with favorable-risk tumor characteristics and younger patients with poor-risk tumor characteristics.[3]

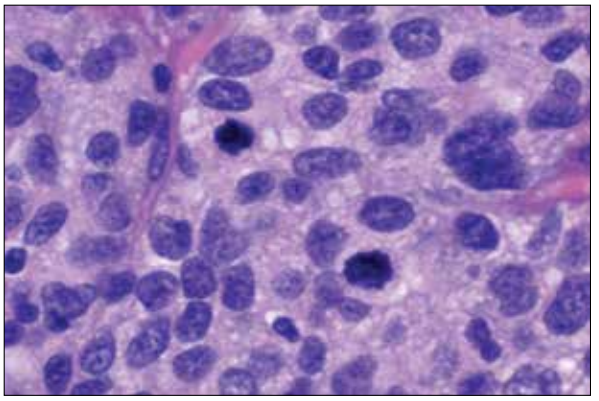

Figure 4. In thyroid cancer, poorly differentiated tumors are typically larger, are associated with gross extrathyroid extensions, result in distant metastases, and are more likely to cause death.

Risk group stratification is the most important clinical parameter for predicting prognosis and for planning treatment, including selecting the extent of initial surgery, the need for adjuvant therapy, and the degree of rigorous follow-up required. The use of these criteria for treatment selection substantially increases the likelihood of providing cost-effective, value-based care. It is important to keep in mind that in low-risk patients, overtreatment increases morbidity without affecting survival.

Surgical Techniques in Thyroid Cancer

There are several important considerations in the surgical treatment of thyroid cancer. First, the only appropriate procedures for patients with proven or suspicious thyroid carcinoma are 2 extracapsular operations: insular thyroid

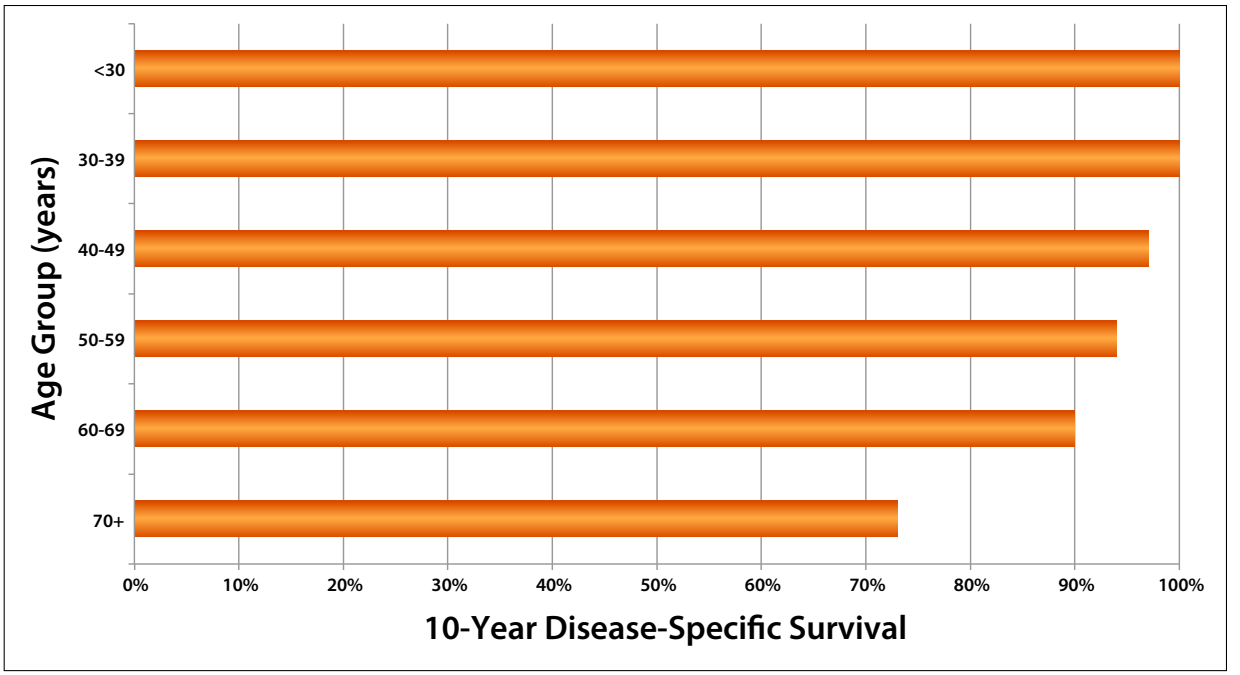

Figure 5. Survival by age in patients with differentiated cancer of the thyroid.

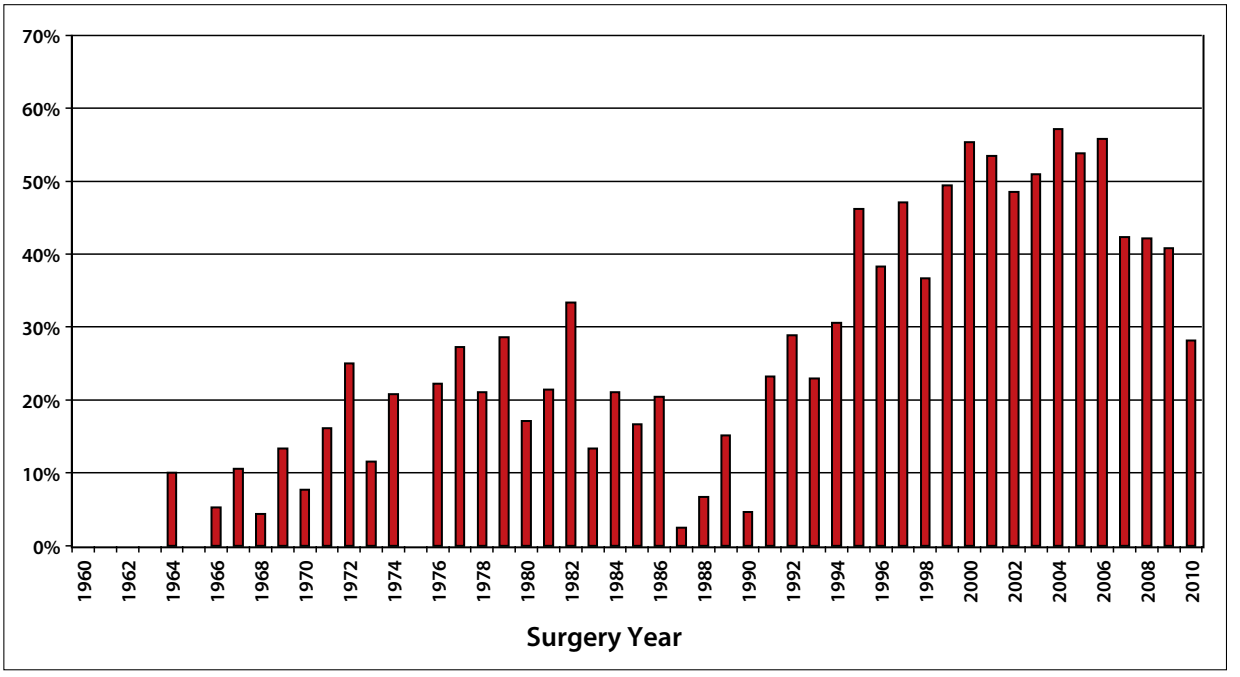

Figure 6. At Memorial Sloan Kettering Cancer Center, the use of radioactive iodine has decreased with the application of more stringent selection criteria.

lobectomy and total thyroidectomy. Subtotal thyroidectomy and near total thyroidectomy are procedures designed for multinodal goiter or thyrotoxicosis rather than for cancer treatment.

At Memorial Sloan Kettering Cancer Center (MSKCC), patients with unifocal intrathyroidal DTC are treated with insular total lobectomy. Thyroidectomy is used for patients with bilateral disease or nodular disease in the contralateral lobe or in the presence of high-risk features, such as histology, age, presence of metastases, gross extrathyroid extension, tumors larger than 4 cm, or previous radiation.

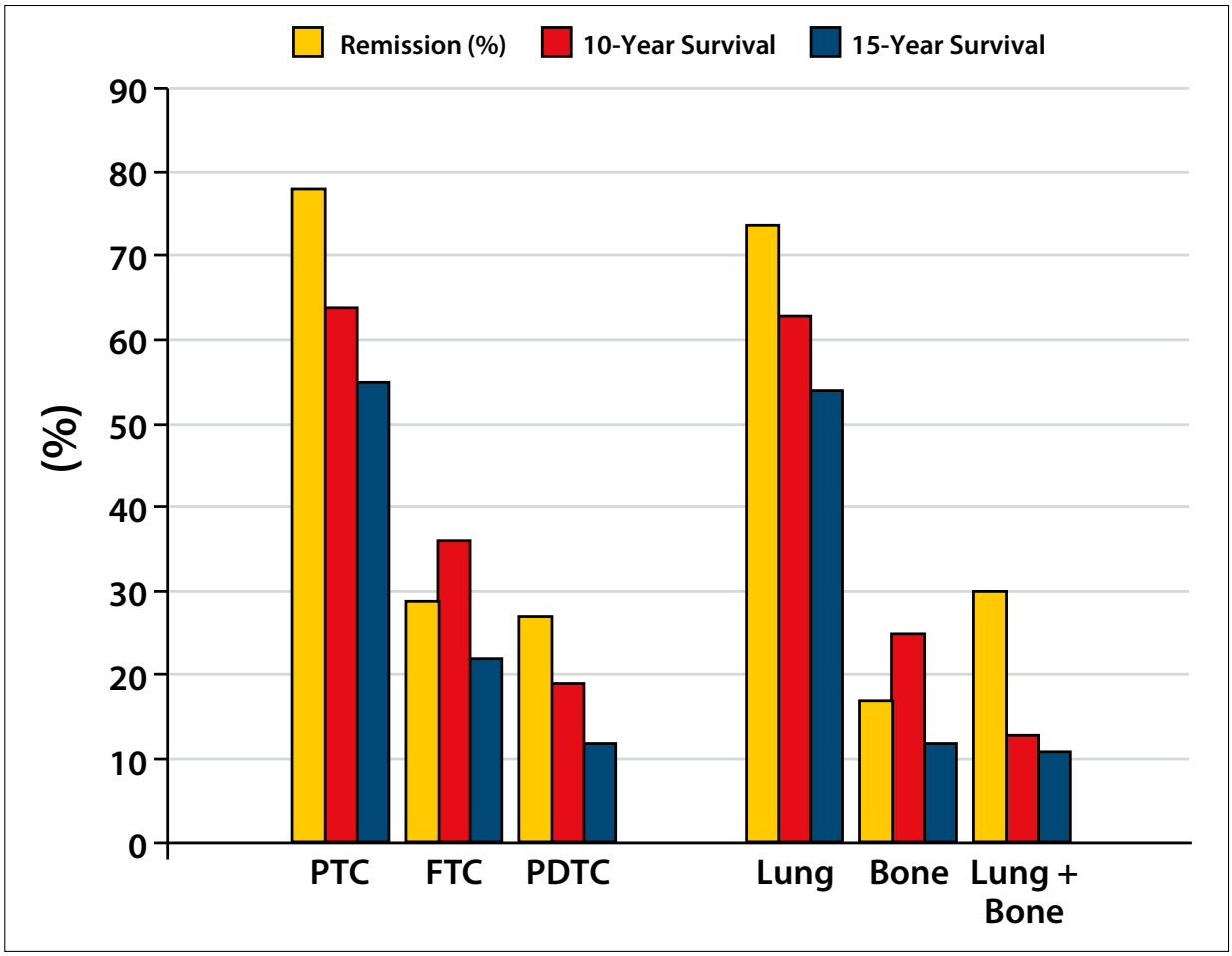

Figure 7. In differentiated thyroid cancer, the response to radioactive iodine varies according to disease subtype and site of metastases. FTC, follicular thyroid cancer; PDTC, poorly differentiated thyroid carcinoma; PTC, papillary thyroid cancer. Adapted from Durante C et al. *J Clin Endocrinol Metab*. 2006;91(8):2892-2899.[7]

Selecting Patients for RAI

The decision to use RAI is influenced by various risk factors, including whether the tumor was completely resected, tumor histology, the presence of extrathyroid extensions, and the presence of nodal and/or distant metastases.[4] There has been a movement away from the routine use of RAI in patients who have undergone a total thyroidectomy in favor of treatment selection based on a variety of factors. ATA guidelines have identified patient-related and disease-related factors that warrant consideration of RAI; they include older age, male sex, tumor size larger than 1 cm, extrathyroid extensions, nodal metastases, and distant metastases.[4] At MSKCC, the decision to use RAI is based on patient age (<45 years vs >45 years), tumor size, and the presence of metastases. The increased application of these selection criteria has led to a decrease in the use of RAI in recent years at MSKCC (Figure 6). In the lowest-risk patients, RAI is not needed; in the highest-risk patients, RAI should always be used. The role of RAI in intermediate-risk patients is less clear.

Estimating Risk of Recurrence

In thyroid cancer, estimating the risk of recurrence is quite different than estimating the likelihood of survival. Some patients will survive but develop local/regional recurrence that adversely affects quality-of-life. In a retrospective analysis of 588 patients with DTC after total thyroidectomy and RAI remnant ablation, persistent structural disease or recurrence developed in 34% of patients with AJCC stage I disease, 51% with stage II disease, 37% with stage III disease, and 62% with stage IV disease.[5]

Other criteria have been developed specifically for estimating the risk of recurrence in patients with thyroid cancer. According to the 2009 criteria developed by the ATA, factors associated with a low risk of recurrence in patients with DTC include classic papillary thyroid car-

cinoma (PTC); no local or distant metastases; complete resection; lack of tumor or vascular invasion; and, if RAI is administered, lack of RAI uptake outside the thyroid bed.[4] Factors associated with intermediate risk include microscopic extrathyroid extension, nodal metastases, aggressive histology, and vascular invasion. Factors associated with a high risk of recurrence include the presence of macroscopic gross extrathyroid extensions, incomplete tumor resection, distant metastases, and inappropriate thyroglobulin elevation. Using these criteria, rates of recurrent/persistent disease are approximately 13% to 14% in patients with a low risk of recurrence, 37% to 44% in intermediate-risk patients, and 85% to 86% in high-risk patients.[5,6]

Recurrent disease can be categorized as structural, which is demonstrable by physical examination, imaging, ultrasound, or CT/MRI; or biochemical, which is indicated by an elevated thyroglobulin level.[5] The likelihood of structural vs biochemical recurrence varies by recurrence risk category. Among patients with low-risk disease, 85% of recurrences are biochemical and 14% are structural.[5] Among intermediate-risk patients, recurrences are biochemical in 55% and structural in 44%. In high-risk patients, 86% of recurrences are structural.

Among patients with metastatic DTC, the site of metastasis affects the likelihood of RAI response. Lung metastases are more responsive to RAI than bone metastases (Figure 7); therefore, the prognosis is more favorable in patients with lung metastases than in patients with bone metastases.[7]

In a 2013 analysis of 171 patients with DTC treated with total thyroidectomy and RAI, after a median of 4 years, remission was attained by 90% of low-risk patients, 76% of intermediate-risk patients, and 41% of high-risk patients.[8] Structural persistence was observed in 3%, 17%, and 48% of patients, respectively, and biochemical persistence was detected in 7%, 7%, and 11% of patients, respectively. Whereas structural disease clearly warrants treatment, the role of re-treatment in biochemical recurrence is uncertain.

In summary, a significant number of patients will have persistent or recurrent RAI-refractory DTC after total thyroidectomy and RAI ablation. Factors associated with the risk of developing RAI-resistant thyroid cancer include TNM stage, risk group category, histology, and location of distant metastases. For patients at high risk of developing RAI-refractory disease, including those with higher-stage disease, poor histology, bone metastases, or large-volume lung metastases, adjuvant treatment is needed to improve outcomes.

Acknowledgment

Dr Shah has no real or apparent conflicts of interest to report.

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Molecular Mechanisms in Thyroid Cancer Biology

Steven I. Sherman, MD

Recent studies have revealed multiple genetic alterations that are relevant in thyroid cancer. In most patients, an activating mutation can now be identified. The most commonly occurring mutations in patients with papillary thyroid cancer are *BRAF* (found in 62% of patients), RAS (13%), and RET/PTC (6.3%).[1] *BRAF* mutations are rarely observed in follicular carcinoma; the more common mutations are in RAS and the activating factors PAX8/PPAR-γ and PTEN.

The most common mutations involved in thyroid cancer lie within a single pathway in which RET/PTC signals activation of RAS, in turn activating *BRAF* and the MAP kinase pathway (Figure 8).[2] The observation that nonoverlapping oncogenic mutations are involved in DTC suggests the possibility of targeting this pathway for therapeutic benefit.

RET/PTC in Thyroid Cancer

When considering potential targets along this canonical pathway, multiple mediators have been considered. RET/PTC was the first of the fusion oncogenes to be identified in thyroid cancer that result in constitutive expression of a tyrosine kinase domain.[3] Although it was predicted that RET/PTC would be a critical mutation in DTC, multiple studies have shown that RET/PTC mutations are rarely detected in patients with advanced DTC, including those with RAI-refractory DTC.[4] Although RET/PTC mutations are more common in radiation-induced PTC, they are usually observed in patients with locoregional disease rather than in patients with distant metastases.[5] RET is closely related to the proangiogenic receptor vascular endothelial growth factor receptor (VEGFR) 2; thus, antiangiogenic compounds that target RET also target VEGFR2.

BRAF in Thyroid Cancer

A broad spectrum of *BRAF* mutations has been identified in thyroid cancer, including V600E and K601 (observed in the follicular variant of papillary cancer). Initial studies suggested that mutated *BRAF* mutation was associated with poor prognosis.[6,7] However, this observation has not been confirmed in subsequent analyses. In a retrospective study of 1849 patients with papillary thyroid cancer, the *BRAF* V600E mutation was associated with shorter survival, but in a multivariate analysis accounting for relevant clinical factors (lymph node metastases, extrathyroidal invasion, and distant metastases), the prognostic value of *BRAF* V600E lost significance.[8] Similarly, in the DECISION (Study of Sorafenib in Locally Advanced Metastatic Patients With Radioactive Iodine Refractory Thyroid Cancer) trial of sorafenib in RAI-refractory DTC, *BRAF* mutation status was not independently associated with outcomes.[9]

Overall, based on the available evidence, *BRAF* mutation status should not be used to make treatment decisions for patients with thyroid cancer. Moreover, in regard to therapeutic targeting, thyroid cancer is relatively refractory to RAF inhibitors. Recent research has provided new insight into signaling differences among thyroid cancer, melanoma, and colorectal cancer that may explain the variability in responses to targeted agents. Thyroid cancer cells demonstrate a unique molecular mechanism of escape from *BRAF* inhibitor therapy.[10]

VEGFR and FGFR Signaling in Thyroid Cancer

Signaling through the vascular endothelial growth factor (VEGF) receptor has been found to be central to the development of cancer (Figure 9). In a process largely driven by the presence of intratumoral hypoxia, VEGF signaling selectively targets vessels for angiogenesis, creating new vasculature for tumor development.[11]

Thyroid cancers are highly vascular, and VEGF is strongly expressed in papillary carcinomas.[12] There is some evidence that VEGF expression is further elevated in *BRAF*-mutant tumors.[13] Moreover, laboratory studies have shown differences in expression of VEGFA, VEGFR, and platelet-derived growth factor (PDGF) β in *BRAF*-wild type vs *BRAF* V600E tumors (Figure 10).[14]

Given the role of angiogenesis in cancer biology, antiangiogenesis has been a significant focus of therapeutic approaches in multiple cancer types. However, clinical experience has shown that angiogenesis inhibitors do not necessarily extend survival.[15] Although VEGF-targeted therapy may reduce growth of primary tumors, it also appears to promote invasiveness and metastasis.[15]

Fibroblast growth factor (FGF) has been identified as a key mechanism contributing to evasive resistance to anti-VEGFR therapy.[16] FGFs, angiopoietins, and ephrins may mediate escape from VEGFR-inhibitor therapy. Thus, there has been interest in combining VEGFR blockade with FGFR blockade to increase the potency

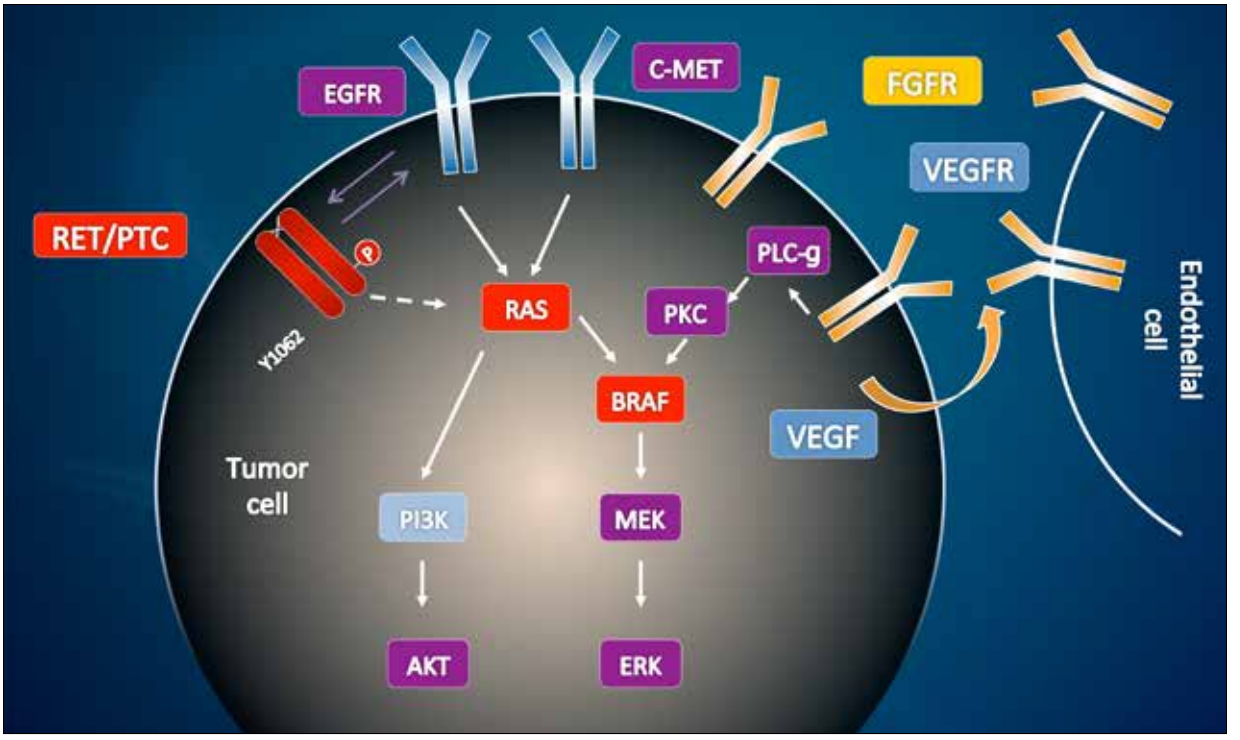

Figure 8. Signaling pathways in differentiated thyroid cancer. FGFR, fibroblast growth factor receptor; VEGF, vascular endothelial growth factor.

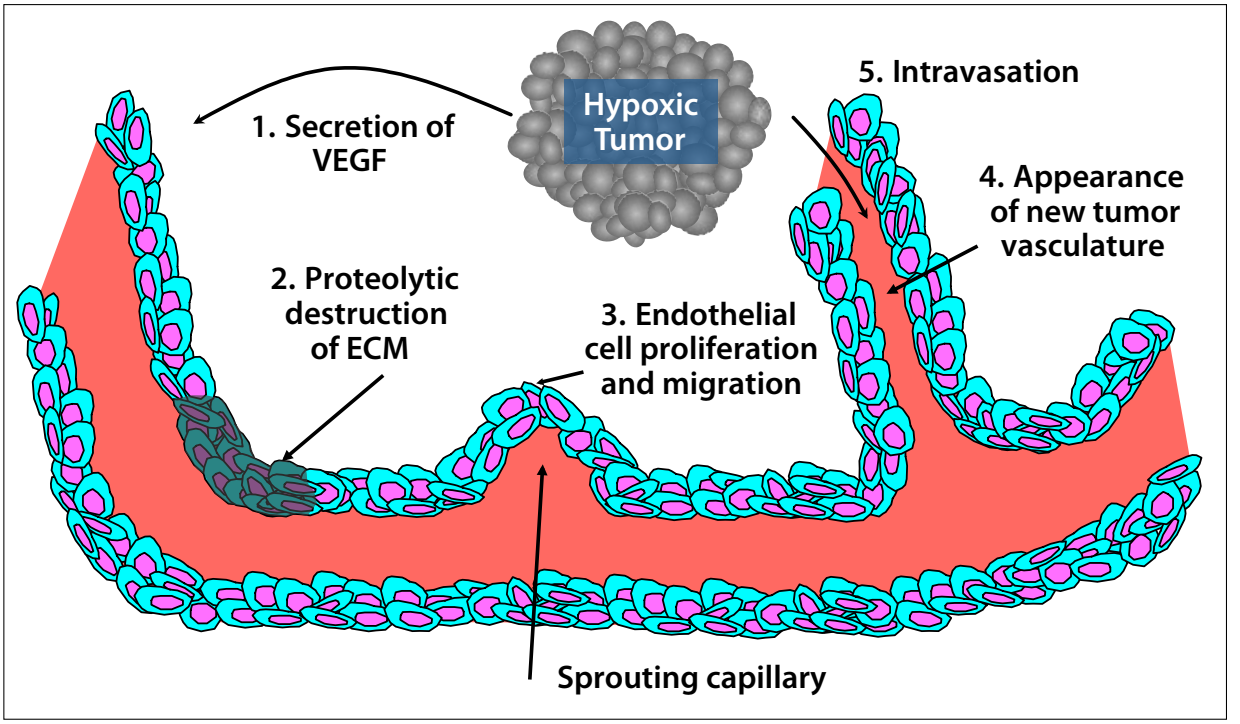

Figure 9. VEGF-mediated angiogenesis. ECM, extracellular matrix; VEGF, vascular endothelial growth factor.

and durability of antiangiogenic therapy. This approach is particularly attractive in thyroid cancer, given that FGFR is usually expressed on the surface of PTC cells. Under normal conditions, thyroid cells express FGFR subtype 2, which induces an antiproliferative pathway.[17] In the setting of papillary thyroid cancer, particularly in tumors with *BRAF* mutations, epigenetic changes cause a switch from FGFR2 to FGFR1, a subtype that promotes

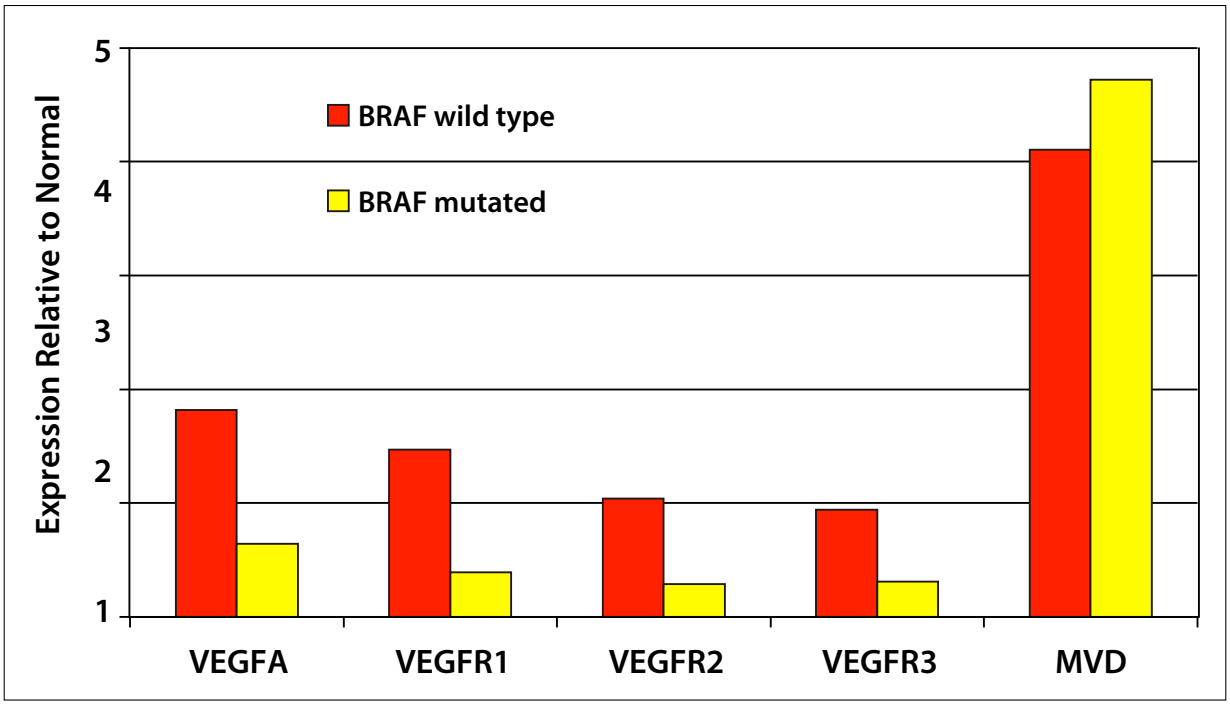

Figure 10. VEGF and angiogenesis in papillary thyroid carcinoma. MVD, microvessel densities; VEGF, vascular endothelial growth factor. Adapted from Durante C et al. *Eur J Endocrinol*. 2011;165(3):455-463.[14]

cell proliferation.[18] Thus, targeting FGFR may provide a dual benefit by both reducing resistance to antiangiogenic therapy and directly targeting cell proliferation through the FGFR pathway.

Platelet-derived growth factor receptor (PDGFR) is also important in thyroid cancer. In papillary thyroid cancer, expression of PDGFR-α is a significant predictor of lymphatic metastases.[19] However, PDGFR does not appear to play a major role in the development of distant metastases.

Early Development of Tyrosine Kinase Inhibitors in Thyroid Cancer

Motesanib diphosphate is an oral inhibitor of VEGF receptors, the PDGF receptor, and KIT. A multicenter phase 2 study demonstrated the activity of motesanib in patients with advanced or metastatic progressive DTC; 14% of patients attained a partial response (PR), and 67% had stable disease.[20] This proof-of-principle study demonstrated the feasibility of conducting multicenter prospective trials in thyroid cancer and demonstrated the clinical activity associated with inhibition of VEGFR and RET. These findings provided a foundation for the later development and evaluation of multi-targeted tyrosine kinase inhibitors in thyroid cancer.

Acknowledgment

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Role of Multi-Targeted Tyrosine Kinase Inhibitors in RAI-Refractory Differentiated Thyroid Cancer

Robert Haddad, MD

The treatment of thyroid cancer has evolved dramatically in recent years. Following a 40-year period during which only 1 drug for thyroid cancer was approved by the US Food and Drug Administration (FDA), 3 drugs—cabozantinib, vandetanib, and sorafenib—were approved in the past 4 years, and additional therapies are on the horizon. The 3 new therapies inhibit multiple targets involved in thyroid cancer biology, including VEGFR and other tyrosine kinases. These agents are providing needed therapies for patients with advanced, progressive, RAI-refractory thyroid carcinoma, who had a poor response to conventional chemotherapy and few other options.

Clinical trials continue to play an important role in advancing the treatment of thyroid cancer; thus, guidelines from the National Comprehensive Cancer Network (NCCN) recommend clinical trials or antiangiogenic tyrosine kinase inhibitors for the treatment of patients with progressive, metastatic, RAI-refractory thyroid cancer.[1]

Sorafenib in Locally Advanced/Metastatic RAI-Refractory DTC

Sorafenib is a multikinase inhibitor targeting VEGFR1-3, PDGF receptors, *BRAF*, RET, and c-Kit. Sorafenib was previously approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma. A series of phase 2 trials demonstrated the efficacy and safety of sorafenib in patients with advanced thyroid cancer.[2-6] Based on the findings in early clinical trials, the randomized, double-blind, placebo-controlled, phase 3 DECISION trial evaluated sorafenib in patients with locally advanced or metastatic RAI-refractory DTC.[7] Eligible patients demonstrated disease progression during the 14 months before enrollment and had not received prior chemotherapy, targeted therapy, or thalidomide. RAI refractoriness was defined as having at least 1 target lesion without iodine uptake or progression following a treatment dose of RAI or a cumulative RAI treatment at or exceeding 600 mCi. Adequate TSH suppression (<0.5 mU/I) was also required for entry. Patients could not be candidates for curative surgery or radiotherapy and were required to have adequate bone marrow, liver, and renal function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

Patients were stratified by geographic region (North America, Europe, or Asia) and age (<60 years vs ≥60 years). They were randomly assigned 1:1 to sorafenib 400 mg (207 patients) or placebo (210 patients), each administered orally twice daily. The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), response rate, safety, time to progression, disease control rate, duration of response, and pharmacokinetics. Progression was assessed every 8 weeks by independent central review. Upon disease progression, patients on the placebo arm could cross over to sorafenib at the investigator's discretion, and patients on the sorafenib arm could continue on open-label sorafenib.

Patient demographics and characteristics were well balanced between the groups. Patients were relatively young,

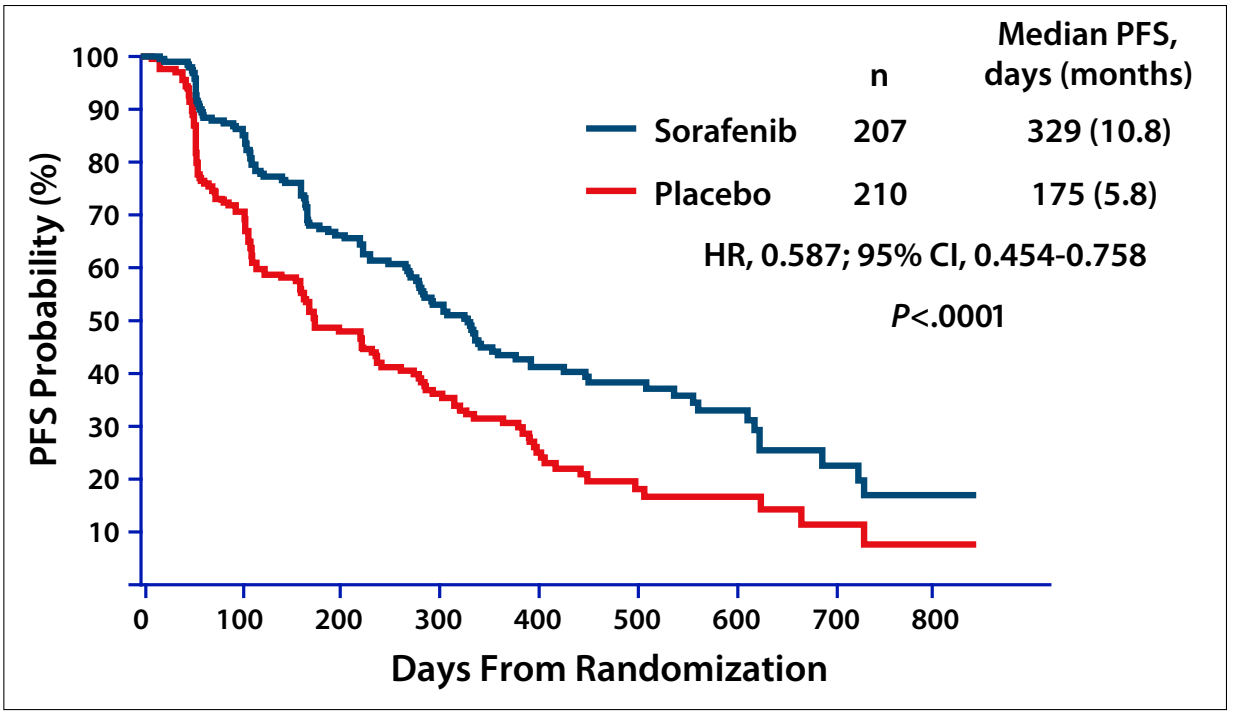

Figure 11. Progression-free survival by independent central review in the DECISION trial of sorafenib vs placebo in patients with locally advanced or metastatic radioactive iodine–refractory differentiated thyroid carcinoma. DECISION, Study of Sorafenib in Locally Advanced Metastatic Patients With Radioactive Iodine Refractory Thyroid Cancer; HR, hazard ratio; PFS, progression-free survival. Adapted from Brose MS et al. *Lancet*. 2014. doi: 10.1016/S0140-6736(14)60421-9.[7]

with a median age of 63 years (range, 24-87 years). Approximately 60% of patients were from Europe, 23% were from Asia, and 17% were from North America. More than 95% of patients had an ECOG performance status of 0 to 1. The patients' most common histologic type was papillary (67%), followed by follicular (24%). Distant metastases were present in 96% of patients; they were most commonly located in the lung (86%), followed by the lymph nodes (51%) and bone (27%). Nearly 100% of patients had undergone prior thyroidectomy, and 42% had received prior locoregional therapy or external beam radiation therapy. The median cumulative RAI activity in the sorafenib and placebo arms was 400 mCi and 376 mCi, respectively.

The DECISION trial demonstrated a significant 5-month improvement in PFS with sorafenib over placebo. Median PFS was 10.8 months for sorafenib vs 5.8 for placebo (hazard ratio [HR], 0.587; 95% CI, 0.454-0.758; *P*<.0001 [Figure 11]).[7] Subgroup analysis demonstrated a PFS benefit with sorafenib across relevant factors, including age group, histology, presence of lung or bone metastases, number of lesions, lesion size, sex, and cumulative RAI dose.

Similar to other recently approved tyrosine kinase inhibitors (TKIs), including vandetanib[8] and cabozantinib,[9] sorafenib was not associated with an improvement in OS as compared with the control arm. There was no significant difference in OS between the arms, and the median OS was not reached in either arm. Upon progression, 71% of patients in the placebo arm switched to open-label sorafenib, and 27% of patients in the sorafenib arm switched to open-label sorafenib.

Sorafenib was associated with an overall response rate (ORR) of 12.2%; these responses were all PRs, with a median duration of 10.2 months (range, 7.4-16.6 months). Another 42% of patients had stable disease for at least 6 months. One PR was observed in a patient on the placebo arm. At least some degree of tumor shrinkage was observed in 73% of patients receiving sorafenib and 27% of patients receiving placebo.

The median duration of treatment in the sorafenib and placebo arms was 46 weeks and 28 weeks, respectively. Adverse events (AEs) resulted in dose modifications in 78% of the sorafenib arm and 30% of the placebo arm, and permanent discontinuation in 19% and 4% of patients, respectively. The most common grade 3/4 AEs observed with sorafenib were hand-foot skin reaction (20.3%), hypertension (9.7%), hypocalcemia (9.2%), diarrhea (5.8%), fatigue (5.8%), and weight loss (5.8%). One drug-related death was reported (0.5%). Some of the AEs observed with sorafenib are class effects, such as hypertension, which is associated with VEGF inhibitors.

The most common adverse events of any grade were hand-foot reaction (76%), diarrhea (68%), alopecia

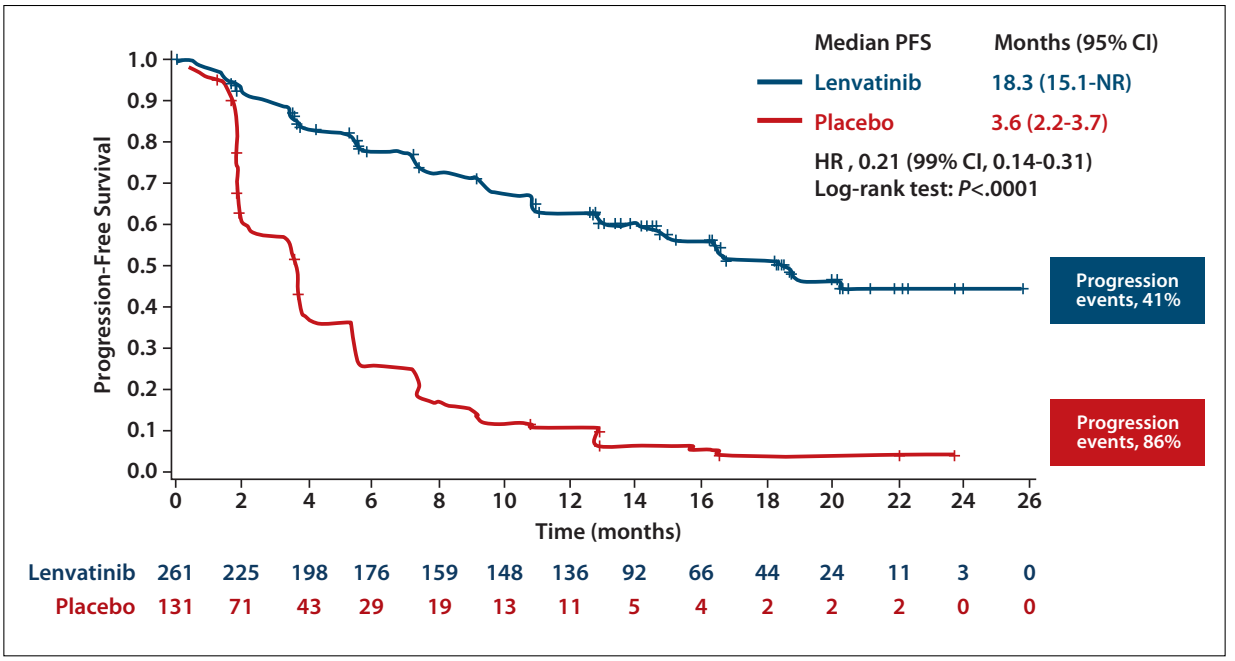

Figure 12. In the SELECT trial of patients with radioactive iodine–refractory differentiated thyroid carcinoma, lenvatinib was associated with an improvement in progression-free survival. HR, hazard ratio; NR, not reached; SELECT, Study of [E7080] Lenvatinib in Differentiated Cancer of the Thyroid. Adapted from Schlumberger M et al. ASCO abstract LBA6008. *J Clin Oncol.* 2014;32:5(suppl).[12]

(67%), rash/desquamation (50%), and fatigue (49.8%). When evaluating the safety profile of sorafenib and other tyrosine kinase inhibitors, it is important to keep in mind that this patient population is often asymptomatic. Therefore, the potentially negative effects of these agents on quality-of-life should be considered.

In summary, the DECISION trial demonstrated a significant improvement in PFS over placebo, and safety results were consistent with previous reports of the safety profile of sorafenib. In November 2013, sorafenib received FDA approval for the treatment of locally recurrent or metastatic progressive DTC refractory to RAI treatment.

Lenvatinib in Locally Advanced/Metastatic RAI-Refractory DTC

Lenvatinib is an orally administered inhibitor of VEGFR1-3, FGFR1-4, PDGFRβ, RET, and KIT. Lenvatinib was first evaluated in a phase 1 study of patients with various solid tumors, including thyroid cancer.[10] The study demonstrated the safety of lenvatinib and identified 24 mg once daily as the recommended dose for future study. Partial responses were observed in 3 of the 5 patients with thyroid cancer. Adverse events included hypertension, proteinuria, fatigue, and gastrointestinal symptoms.

Subsequently, a phase 2 trial was undertaken evaluating lenvatinib in 58 patients with advanced RAI-refractory DTC.[11] In this study, lenvatinib was associated with an ORR of 59% (all PRs). The ORR was 63% in the subset of patients with no prior VEGFR-targeted therapy and 47% in the subset of patients previously treated with VEGFR-targeted therapy. Lenvatinib was associated with a median PFS of 13.3 months, which was considered promising.

Based on the safety and activity demonstrated in the phase 2 study, the randomized, double-blind, placebo-controlled phase 3 SELECT (Study of [E7080] Lenvatinib in Differentiated Cancer of the Thyroid) trial was undertaken evaluating lenvatinib in patients with RAI-refractory DTC. Results of the SELECT trial were presented at the 2014 Annual Meeting of the American Society of Clinical Oncology.[12] The trial enrolled 392 patients with RAI-refractory disease that had progressed within the past 13 months. Whereas the DECISION trial of sorafenib did not allow a prior targeted agent, the SELECT trial was open to patients who had received up to 1 prior VEGF/VEGFR-targeted agent. Stratification was based on geographic region (Europe, North America, or other), prior VEGF/VEGFR-targeted therapies (0 vs 1), and age (≤65 years vs >65 years).

Patients were randomly assigned 2:1 to lenvatinib 24 mg (261 patients) or placebo (131 patients), each administered once daily until disease progression as confirmed by an independent review. Patients in the control arm could cross over to open-label lenvatinib upon disease progression. The primary endpoint was PFS; secondary endpoints included ORR, OS, and safety.

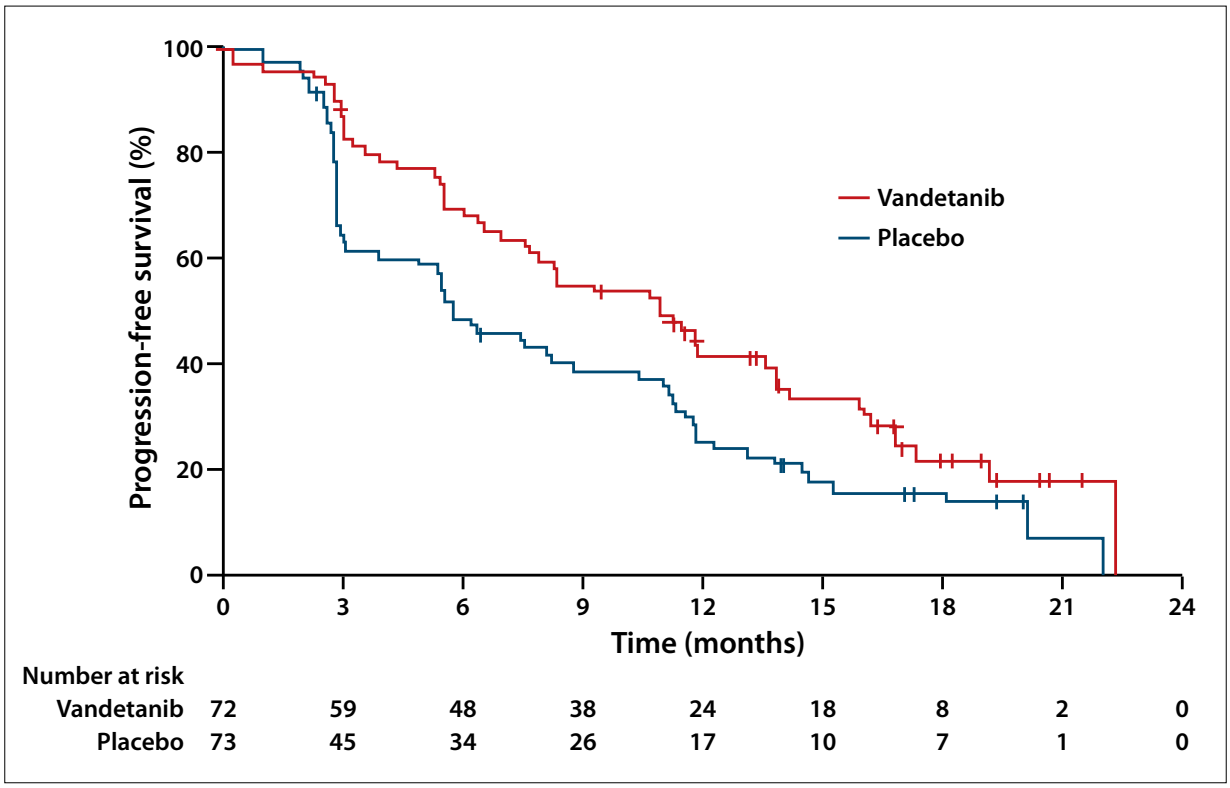

Figure 13. Kaplan-Meier estimates of progression-free survival in a phase 2 study comparing vandetanib vs placebo in patients with locally advanced or metastatic radioactive iodine–refractory differentiated thyroid carcinoma. Adapted from Leboulleux S et al. *Lancet Oncol.* 2012;13(9):897-905.[8]

Baseline characteristics were well balanced between the arms. The median age was 64 years in the lenvatinib arm and 61 years in the placebo arm. Approximately half of patients were from Europe, 30% were from North America, and 20% were from other locations in South America, Asia, and Russia. Prior VEGF-targeted therapy had been administered in 25% of patients in the lenvatinib arm and 21% in the placebo arm. Pulmonary metastases were present in 87% of patients in the lenvatinib arm and 95% in the placebo arm.

The SELECT trial demonstrated a significant improvement in PFS with lenvatinib over placebo, with a median PFS of 18.3 months vs 3.6 months, respectively (HR, 0.21; 95% CI, 0.14-0.31; *P*<.0001; Figure 12). This degree of PFS improvement is rarely observed in a medical oncology trial. The PFS improvement with lenvatinib was observed regardless of whether patients received prior VEGF-targeted therapy. Among the 299 patients who had not received a prior VEGF-targeted agent, the median PFS was 18.7 months with lenvatinib and 3.6 months with placebo (HR, 0.20; 95% CI, 0.14-0.27; *P*<.0001). Among the 93 patients who had previously received a VEGF-targeted agent, the median PFS was 15.1 months with lenvatinib and 3.6 months with placebo (HR, 0.22; 95% CI, 0.12-0.41; *P*<.0001). As in the DECISION trial, the SELECT trial found no significant difference in OS between the arms, which was attributed primarily to the crossover allowed on the placebo arm.

Lenvatinib was associated with a high ORR of 65%, including 2% complete responses. Another 15% of patients had stable disease for at least 23 weeks. The median duration of response was not reached, indicating that patients attained durable responses with lenvatinib. The median time to response was 2.0 months (range, 1.9-3.5 months). Tumor shrinkage was observed in the majority of patients on the lenvatinib arm; the median change in size of target lesions among responding patients on the lenvatinib arm was -52%.

Lenvatinib was associated with treatment-related AEs that resulted in dose reductions in 68% of patients, dose interruptions in 82%, and treatment discontinuation in 14%. Among the 20 deaths due to AEs, 6 were attributed to therapy, for a treatment-related mortality rate of 2%. Four of the deaths were from general health deterioration, 1 from pulmonary embolism, and 1 from hemorrhagic stroke.

The most frequent treatment-related AE was hypertension, which occurred in 68% of patients and was grade 3 or higher in severity in 42%. Hypertension is easily managed but must be addressed properly. The other most common grade 3 or higher AEs were decreased weight

(10%) and proteinuria (10%). Other common AEs of any severity included diarrhea (60%), fatigue (59%), decreased appetite (50%), nausea/vomiting (46%), and decreased weight (46%).

In summary, in the SELECT trial, lenvatinib was associated with a significant 14.7-month improvement in PFS compared with placebo. The 65% ORR observed in the SELECT trial was substantially higher than the 12% response rate observed in the DECISION trial of sorafenib. Lenvatinib was also associated with significant toxicities, including the potential for fatal AEs, which should be taken into consideration, particularly as the agent has not yet demonstrated a survival benefit. Medical oncologists and endocrinologists must be familiar with the toxicity profile of lenvatinib so that AEs are managed appropriately. Although lenvatinib is not yet commercially available, it will likely be submitted for regulatory approval soon.

Vandetanib in RAI-Refractory DTC

Vandetanib, a multikinase inhibitor currently approved for patients with medullary thyroid cancer, has also been evaluated in patients with DTC. A randomized, double-blind, phase 2 study compared vandetanib vs placebo in patients with locally advanced or metastatic RAI-refractory DTC (papillary, follicular, or poorly differentiated).[8] A total of 145 patients were randomly assigned to vandetanib 300 mg/day (72 patients) or placebo (73 patients). Crossover to vandetanib was allowed upon disease progression for patients in the placebo arm.

A relatively high proportion of patients in the vandetanib trial had poorly differentiated carcinoma (47% in the vandetanib arm and 44% in the placebo arm), reflecting a more aggressive histology. Vandetanib was associated with an ORR of 8% and a median PFS of 11.1 months, compared with 5.9 months with placebo (Figure 13). The most frequent grade 3 or higher AEs observed with vandetanib were QTc prolongation (10%), asthenia (7%), and fatigue (5%). The randomized, double-blind, placebo-controlled phase 3 VERIFY (Evaluation of Efficacy, Safety of Vandetanib in Patients With Differentiated Thyroid Cancer) trial is currently evaluating vandetanib in patients with locally advanced or metastatic DTC that is refractory to, or unsuitable for, RAI therapy.[13]

mTOR Inhibitors in Thyroid Cancer

The mammalian target of rapamycin (mTOR) inhibitor everolimus is also being evaluated in thyroid cancer treatment. A phase 2 trial evaluated the efficacy and safety of everolimus in patients with aggressive RAI-refractory thyroid cancer.[14] The patient population included a main cohort of 33 patients with DTC and exploratory cohorts of 10 patients with medullary thyroid cancer and 7 patients with anaplastic thyroid cancer. Patients were required to have had disease progression within 6 months before enrollment.

Among 31 evaluable patients, everolimus was associated with a median PFS of 16.0 months. Disease stability was maintained for at least 6 months in 18 patients (58%) and for at least 12 months in 10 patients (32%). Median OS was not reached, and the 1-year OS rate was 76%. There is interest in pursuing everolimus in a larger trial.

BRAF-Targeted Therapy in Thyroid Cancer

The *BRAF* inhibitor vemurafenib has been evaluated in the setting of *BRAF*-mutated, RAI-refractory papillary thyroid cancer. A phase 2 study evaluated vemurafenib in 51 patients with *BRAF* mutations (26 VEGFR TKI-naive patients and 25 VEGFR TKI-exposed patients).[15] Patients were required to have measurable disease with progression in the previous 14 months before enrollment. Vemurafenib was associated with an ORR of 35% in VEGFR TKI-naive patients and 26% in VEGFR TKI-exposed patients. The clinical benefit rate (including patients with stable disease ≥6 months) was 58% in VEGFR TKI-naive patients and 36% in VEGFR TKI-exposed patients, and the median PFS was 15.6 months and 6.8 months, respectively.

The safety profile with vemurafenib reflected previous reports in melanoma, and AEs included weight loss; dysgeusia; anemia; elevated creatinine; elevated liver laboratory abnormalities, including bilirubin; rash; and fatigue.[15]

Conclusion

Although RAI-refractory DTC continues to present a clinical challenge, there are several new agents available, including sorafenib, which was recently approved based on a PFS benefit,[7] and lenvatinib, which also showed a PFS benefit over placebo.[12] Many other agents are currently in phase 3 studies, and therefore the treatment options for these patients may continue to expand.

It is also important to keep in mind that DTC can take an indolent course, and many patients will not require immediate therapy. The decision to initiate therapy should be based on careful clinical judgment; rapidly growing disease and symptomatic disease could both be indications for treatment. Once the decision is made to initiate therapy, patients must be monitored carefully to detect any drug-related toxicities, which can be significant. If AEs do occur, therapy should not be discontinued unnecessarily at the first sign of toxicity. Appropriate AE management may allow patients to continue therapy for an extended period of time.

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Considerations for Initiating Treatment in Advanced Thyroid Cancer

Lori J. Wirth, MD

Outcomes for patients with thyroid cancer are usually favorable. However, approximately 10% to 15% of patients with DTC develop advanced disease, and the outcome for these patients varies. In an analysis of 444 patients with metastatic DTC receiving RAI, 68% of patients attained responses to RAI; the 10-year OS rate among these patients was 92%.[1] Among the remaining 32% of patients with RAI-refractory DTC, the 10-year OS rate was only 10%. Moreover, within the group of patients with RAI-refractory disease, survival rates varied substantially among patients based on the degree of RAI uptake (Figure 14).

Even after adjusting for RAI sensitivity, there is still variability in outcomes among patients with advanced, RAI-refractory DTC. Positron emission tomography (PET) scanning can help differentiate between aggressive and less aggressive disease; greater FDG avidity is associated with poorer outcomes.[2] Therefore, there is considerable clinical heterogeneity among thyroid cancers. This variability is reflected in multiple genotypic and phenotypic factors, including histology, genotype, tumor size, extent of extrathyroid extension, and number of lymph node metastases. These findings can all help predict prognosis.

Until the advent of targeted agents, therapeutic options were limited for patients with advanced DTC, and cytotoxic chemotherapy was relatively ineffective. The era of cytotoxic chemotherapy drugs is now over, as a new class of drugs is available, with sorafenib, vandetanib, and lenvatinib all demonstrating a clear PFS benefit over placebo.[3-5]

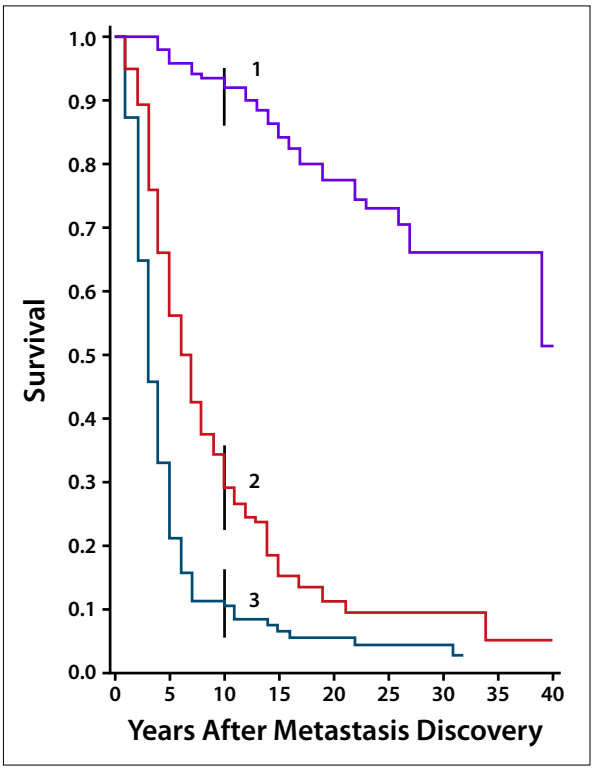

Figure 14. Survival after discovery of metastasis in thyroid carcinoma patients. Group 1 showed RAI uptake and attained negative imagining. Group 2 showed RAI uptake but did not attain negative imagining. Group 3 had no RAI uptake. RAI, radioactive iodine. Adapted from Durante C et al. *J Clin Endocrinol Metab*. 2006;91(8):2892-2899.[1]

When to Start Therapy

Clinical trial data suggest that targeted agents could be effective in many patients; subset analyses have indicated a PFS benefit across subgroups for these agents.[3-5] For patients with progressive disease requiring an active agent, targeted agents have demonstrated substantial activity. Although several agents have not demonstrated high response rates, the 65% ORR reported with lenvatinib, with a median change in tumor size of -52% among responders, indicates significant antitumor activity (Figure 15).[5]

The demonstration of a significant survival benefit could help guide the treatment decision, particularly in the case of indolent disease. In the absence of a demonstrated OS benefit, the decision to initiate treatment can be unclear. The median OS has not been reached for the sorafenib or vandetanib trials.[3,4] In the SELECT trial of lenvatinib, although the median OS has not been reached, the survival curves for lenvatinib and placebo appear to be separating, suggesting the possibility of an emerging survival benefit.[5] However, crossover will be a substantial limitation in detecting a survival difference.

The risk of AEs must also be weighed in the decision to initiate therapy. The toxicity profiles of the tyrosine kinase inhibitors cannot be minimized. There are differences among the agents. For example, sorafenib is

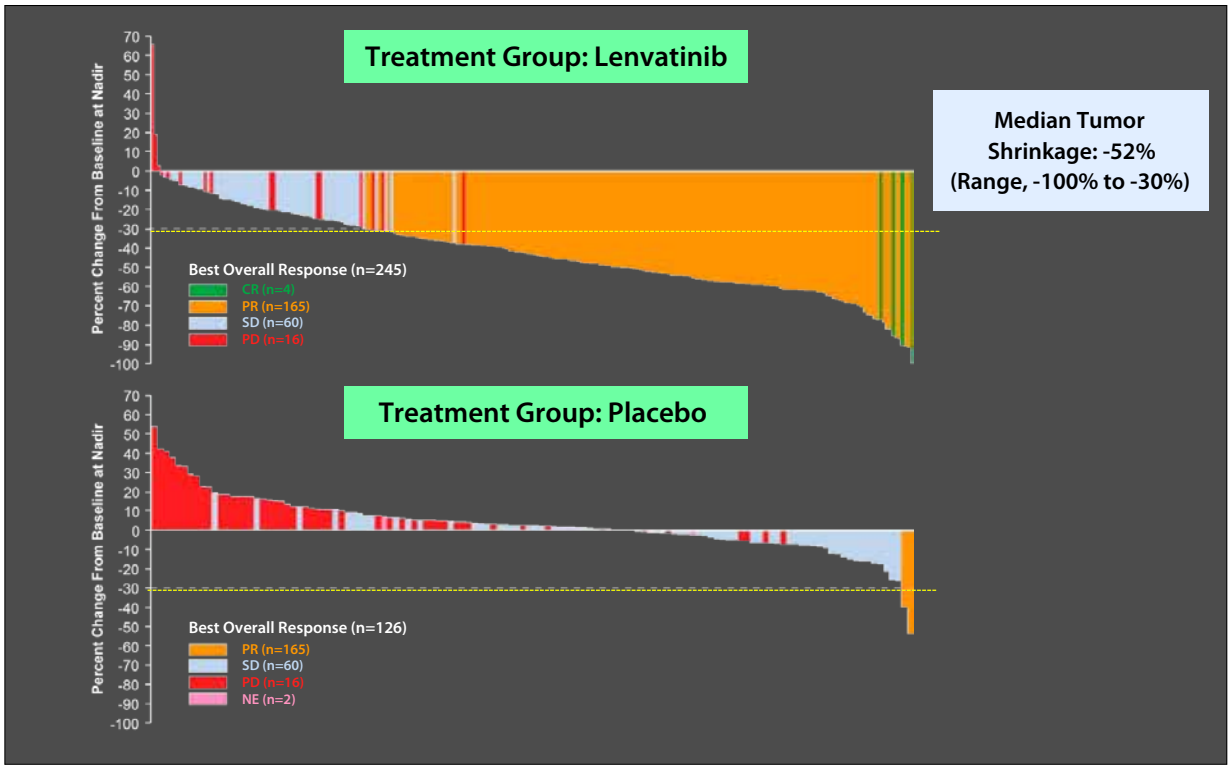

Figure 15. In the SELECT trial, lenvatinib was associated with an overall response of 65% and a median change in tumor size of -52% among responders, indicating significant antitumor activity. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; SELECT, Study of [E7080] Lenvatinib in Differentiated Cancer of the Thyroid; VEGF, vascular endothelial growth factor. Adapted from Schlumberger M et al. ASCO abstract LBA6008. *J Clin Oncol.* 2014;32:5(suppl).[5]

associated with more hand-foot skin reaction (76%) and alopecia (67%),[3] whereas lenvatinib is associated with more hypertension (68%).[5] Diarrhea is common with both agents.[3,4] Rarely, VEGFR multikinase inhibitors can be associated with life-threatening AEs, including cardiac ischemia and/or myocardial infarction, bleeding, venous thromboembolic events, gastrointestinal perforation, and aerodigestive fistula formation.[3,4,6]

Quality-of-life data could be helpful in guiding the decision to initiate treatment. Unfortunately, there are few data evaluating quality-of-life in this setting. However, the DECISION trial of sorafenib did report on several patient-reported outcomes. Notably, the quality-of-life measurements at baseline in the DECISION trial were typical of those observed in trials of patients with solid tumors.[7] Patients with thyroid cancer are typically considered to have indolent, asymptomatic disease, but the patients enrolling in trials of progressive, RAI-refractory disease are often unwell, with the disease affecting quality-of-life at study entry. In the DECISION trial, quality-of-life scores remained stable in the placebo arm but declined slightly in the sorafenib arm, providing evidence of the potential negative effects of therapy on quality-of-life.[7]

The potential effects of treatment on quality-of-life should be a factor in the treatment-decision process, particularly in the setting of advanced, RAI-refractory thyroid cancer, in which complete responses are uncommon. If clinicians were able to offer a potentially curative therapy, in particular one involving therapy administered for a discrete amount of time, patients might be more willing to endure AEs. However, in the context of a noncurative therapy, the toxicity profile—including the potential effects of therapy on the ability of patients to maintain their daily activities—is important to consider.

Overall, multiple factors should be weighed in the decision to initiate therapy. First is the nature of the disease, including the rate of progression. The phase 3 trials of advanced RAI-refractory DTC required progression throughout the previous 12 to 14 months for clinical trial entry. The burden of disease and any symptoms should also be considered. Another factor is the presence of comorbidities, including complications from thyroidectomy. Patient preference is important; some patients would rather not start therapy unless absolutely necessary, whereas others may have anxiety about not treating the cancer and would prefer to start treatment earlier rather than later.

Implementing Targeted Therapy in Thyroid Cancer

When the decision has been made to start a targeted agent, in most patients, it is important to initiate therapy at the recommended dose level. One exception is elderly patients with multiple comorbidities. Toxicities, which occur frequently with these agents, should be managed with dose interruptions and/or sequential dose reductions. In some cases, specific management recommendations are provided for individual AEs that may develop. Although dose modifications are sometimes required, it is also important to not reduce dosages unnecessarily. Appropriate supportive care may allow a patient to maintain a dosage.

Responses to targeted agents should be assessed via imaging every 2 to 3 cycles (2-3 months), using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. In patients with measurable disease, thyroglobulin levels should be assessed when restaging is performed. Although thyroglobulin levels may be associated with response, they are not usually used to inform the treatment decision. In general, treatment is continued until disease progression per RECIST 1.1 or until the development of unacceptable toxicity.

It is important to follow patients carefully after they begin treatment with a TKI. Adverse events, such as hypertension, can develop early, within the first 2 weeks of therapy. Therefore, for the first 2 months, patients should be evaluated every 2 weeks with a physical examination; blood pressure monitoring; laboratory assessments to assess blood, kidney, and liver parameters; and urinalysis to check for proteinuria. TSH levels should also be monitored, as TKIs can result in TSH elevations requiring dose adjustments in levothyroxine in order to maintain TSH suppression. EKG assessments are also appropriate to monitor for the development of QTc interval prolongations.

Ongoing Issues and Future Directions

VEGFR multikinase inhibitors have significant clinical activity for this patient population that previously lacked good options. However, there are several unanswered questions regarding the role of these therapies. First, the optimal sequence of individual agents has not been evaluated. Head-to-head trials of targeted agents will not necessarily be conducted, yet, given the heterogeneity of the disease, caution must be exercised when comparing agents across trials. Lenvatinib has demonstrated robust activity, including in the second-line setting after a TKI.[5] Given the extent of PFS improvement observed with lenvatinib, it may be more appropriate to use this agent first. A second question concerns whether PFS correlates with OS. Third, the effects of newer therapies on quality-of-life are not well understood, and therefore studies evaluating this measure are needed.

A proportion of patients with advanced RAI-refractory DTC will require immediate treatment. When therapy is initiated, toxicities occur frequently and require intensive monitoring and aggressive management to allow patients to stay on therapy for as long as possible.

Acknowledgment

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New Frontiers and Treatment Paradigms for Thyroid Carcinoma

CME Post-Test: *Circle the correct answer for each question below.*

1. From 2001 to 2010, the proportion of patients with thyroid carcinoma who died from the disease:

   a. Decreased by approximately 33%
   b. Decreased by approximately 16%
   c. Increased by approximately 13%
   d. Increased by approximately 28%

2. Total thyroidectomy is optimal for most patients with tumors ≥1 cm in diameter.

   a. True
   b. False

3. All of the following patient/tumor factors should prompt consideration of radioactive iodine (RAI) therapy, EXCEPT:

   a. Female patient
   b. Tumor size >1 cm
   c. Extrathyroid extension
   d. Presence of metastases

4. Which factor is NOT associated with a high risk of recurrence in patients with differentiated thyroid cancer?

   a. Distant metastases
   b. Inappropriate thyroglobulin elevation
   c. Incomplete tumor resection
   d. Microscopic extrathyroid extension

5. BRAF mutation status should be used to make treatment decisions for patients with thyroid cancer.

   a. True
   b. False

6. What does the National Comprehensive Cancer Network recommend for the treatment of patients with progressive, metastatic, RAI-refractory thyroid cancer?

   a. Clinical trials
   b. Antiangiogenic tyrosine kinase inhibitors
   c. Either clinical trials or antiangiogenic tyrosine kinase inhibitors
   d. Neither clinical trials nor antiangiogenic tyrosine kinase inhibitors

7. Which of the following agents is currently approved in the United States for patients with RAI-refractory differentiated thyroid cancer?

   a. Lenvatinib
   b. Sorafenib
   c. Vandetanib
   d Vemurafenib

8. Which of the following statements regarding sorafenib and the DECISION trial is FALSE?

   a. Sorafenib significantly improved progression-free survival (PFS) and extended PFS by 5 months vs placebo (10.8 vs 5.8 months)
   b. The most common adverse events associated with sorafenib include hand-foot skin reactions, diarrhea, and alopecia
   c. In the sorafenib arm, dose reductions were required by more than 60%, and almost 20% discontinued therapy
   d. Reductions in target lesions were comparable to placebo

9. Which of the following statements from the phase III SELECT trial (Study 303) of lenvatinib is FALSE?

   a. There was a significant improvement in median PFS by nearly 15 months with lenvatinib over placebo (18.3 vs 3.6 months)
   b. The PFS improvement with lenvatinib was observed only in patients who had not received prior vascular endothelial growth factor–targeted therapy
   c. Lenvatinib was associated with an overall response rate of 65%, including 2% complete responses
   d. The most frequent treatment-related adverse event was hypertension

10. In a phase 2 study comparing vandetanib vs placebo in patients with locally advanced or metastatic RAI-refractory differentiated thyroid cancer (papillary, follicular, or poorly differentiated), what was the PFS associated with vandetanib?

    a. 11.1 months
    b. 12.3 months
    c. 13.2 months
    d. 14.5 months

Project ID: 10149

Evaluation Form: New Frontiers and Treatment Paradigms for Thyroid Carcinoma

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 10149**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

1. What degree best describes you?

❒ MD/DO ❒ PA/PA-C ❒ NP ❒ RN ❒ PharmD/RPh ❒ PhD
❒ Other, please specify:

2. What is your area of specialization?

❒ Oncology, Hematology/Oncology ❒ Oncology, Medical
❒ Oncology, Radiation ❒ Oncology, Other

3. Which of the following best describes your *primary* practice setting?

❒ Solo Practice ❒ Group Practice ❒ Government
❒ University/teaching system ❒ Community Hospital
❒ HMO/managed care ❒ Non-profit/community ❒ I do not actively practice
❒ Other, please specify:

4. How long have you been practicing medicine?

❒ More than 20 years ❒ 11-20 years ❒ 5-10 years ❒ 1-5 years
❒ Less than 1 year ❒ I do not directly provide care

5. Approximately how many patients do you see each week?

❒ Less than 50 ❒ 50-99 ❒ 100-149 ❒ 150-199 ❒ 200+
❒ I do not directly provide care

6. How many patients do you currently see each week with thyroid carcinoma?

❒ Fewer than 5 ❒ 6-15 ❒ 16-25 ❒ 26-35 ❒ 36-45 ❒ 46-55
❒ 56 or more ❒ I do not directly provide care

7. Rate how well the activity supported your achievement of these learning objectives:

Identify thyroid cancer patients who are refractory to radioactive iodine
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Employ risk group stratification to predict prognosis and plan treatment
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Describe the clinical significance of molecular pathways targeted by multikinase inhibitors
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Evaluate the latest clinical trial data supporting the use of tyrosine-kinase inhibitors in iodine-refractory thyroid carcinoma
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Apply strategies to manage the adverse events associated with novel targeted therapies for thyroid carcinoma
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The content was evidence based
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The educational material provided useful information for my practice
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity enhanced my current knowledge base
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

9. Based upon your participation in this activity, do you intend to change your practice behavior? *(choose only one of the following options)*

❒ I do plan to implement changes in my practice based on the information presented
❒ My current practice has been reinforced by the information presented
❒ I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? *(check all that apply)*

❒ Apply latest guidelines ❒ Choice of treatment/management approach
❒ Change in pharmaceutical therapy ❒ Change in current practice for referral
❒ Change in nonpharmaceutical therapy ❒ Change in differential diagnosis
❒ Change in diagnostic testing ❒ Other, please specify:

12. How confident are you that you will be able to make your intended changes?

❒ Very confident ❒ Somewhat confident ❒ Unsure ❒ Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

❒ Formulary restrictions ❒ Insurance/financial issues ❒ Time constraints
❒ Lack of multidisciplinary support ❒ System constraints
❒ Treatment-related adverse events ❒ Patient adherence/compliance
❒ Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

❒ Yes ❒ No, please explain:

15. Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

Request for Credit (*required fields)

Name* _____

Degree* _____

Organization _____

Specialty* _____

City, State, ZIP* _____

Telephone _____ Fax _____

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For Physicians Only:

I certify my actual time spent to complete this educational activity to be:

❒ I participated in the entire activity and claim 1.25 credits.
❒ I participated in only part of the activity and claim _____ credits.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Project ID: **10149**