

Lenvatinib in Advanced, Radioactive Iodine-Refractory, Differentiated Thyroid Carcinoma

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Abstract

Management options are limited for patients with radioactive iodine refractory, locally advanced, or metastatic differentiated thyroid carcinoma. Prior to 2015, sorafenib, a multitargeted tyrosine kinase inhibitor, was the only approved treatment and was associated with a median progression-free survival (PFS) of 11 months and overall response rate (ORR) of 12% in a phase III trial. Lenvatinib, a multikinase inhibitor with high potency against VEGFR and FGFR demonstrated encouraging results in phase II trials. Recently, the pivotal SELECT trial provided the basis for the FDA approval of lenvatinib as a second targeted

therapy for these patients. Median PFS of 18.3 months in the lenvatinib group was significantly improved from 3.6 months in the placebo group, with an HR of 0.21 (95% confidence interval, 0.4–0.31; $P < 0.0001$). ORR was also significantly increased in the lenvatinib arm (64.7%) compared with placebo (1.5%). In this article, we will review the molecular mechanisms of lenvatinib, the data from preclinical studies to the recent phase III clinical trial, and the biomarkers being studied to further guide patient selection and predict treatment response. *Clin Cancer Res*; 21(24); 5420–6. ©2015 AACR.

Introduction

Thyroid carcinoma is the most common endocrine malignancy, with an estimated incidence rate of 13.5 per 100,000 people per year and a prevalence of approximately 600,000 people in the United States (1). Differentiated thyroid carcinoma (DTC) is a heterogeneous group which includes papillary (PTC), follicular, Hurthle cell, and poorly differentiated histologies. Despite generally good prognosis and cure rates of DTC with surgery, radioactive iodine (RAI) therapy, and thyroid stimulating hormone suppressive therapy, 10% to 20% of patients will develop recurrent or metastatic disease. Those who respond to RAI have excellent 10-year survival, but a minority will have poor survival of less than 5 years due to RAI-refractory, metastatic, aggressive disease. This review will focus on the recent approval of lenvatinib for the patient subset with locally recurrent or metastatic, RAI refractory DTC. The molecular pathways involved in tumorigenesis of DTC will be briefly reviewed. Other selected targeted therapies will also be mentioned for historical comparison.

Aberrant Molecular Pathways

Cancers evolve through a multistep tumorigenic process with alternations in crucial signaling pathways. Thyroid carcinoma is no exception. In fact, almost all (>96%) PTCs have at least one driver genomic alteration found in The Cancer Genome Atlas (TCGA; ref. 2). Thyroid cancer has a low density of somatic mutations and most aberrancies involve the MAPK and the

PI3K–mTOR pathways (reviewed in ref. 3). The signals ultimately converge in the nucleus, influencing transcription of oncogenic proteins including, but not limited to, NF- κ B), hypoxia-induced factor 1 alpha unit (HIF1 α), TGF β , VEGF, and FGF. This leads to enhanced tumor proliferation, differentiation, survival, angiogenesis, invasion, and metastasis (Fig. 1). Genetic alterations in this pathway are usually mutually exclusive and thus supporting their dominant role of tumorigenesis.

Binding of growth factors to transmembrane receptor tyrosine kinase (RTK) such as ret proto-oncogene (RET), platelet-derived growth factor receptor (PDGFR), EGFR, stem cell factor receptor (SCFR), or also known as cKIT, FGFR, or VEGFR results in receptor dimerization and autophosphorylation. Through a series of adaptor proteins, rat sarcoma (RAS) is activated and B-Raf proto-oncogene serine threonine kinase (BRAF) is recruited and activated at the plasma membrane. Activated BRAF then phosphorylates MAPK/extracellular regulated MAPK (ERK) kinase (MEK) which in turn phosphorylates and activates ERK. ERK translocates into nucleus where it stimulates transcription of genes involved in cell proliferation, differentiation, and survival.

The PI3K–mTOR pathway is a parallel signaling pathway with cross talk with the MAPK pathway. PI3K can be activated by either RTK or RAS. Activated PI3K then activates alpha serine/threonine protein kinase (AKT) which activates mTOR. mTOR then translocates into the nucleus and affects transcription of genes related to cell growth, angiogenesis, cell motility, and invasion.

On the basis of the recently published TCGA data on more than 400 PTCs, genomic alterations can be divided into two major clusters that are dominated by either BRAF V600E or RAS mutations. BRAF V600E-like PTCs (BVL-PTCs) carry aberrancies including BRAFV600E, or fusions of BRAF or RET, and anaplastic lymphoma kinase (ALK). They represent a heterogeneous subset, enriched for classical and less differentiated tall cell histologic subtype of PTC, with advanced stage and higher recurrence risk, and predominately activating MAPK signaling. BVL-PTCs is associated with high levels of expression of genes downstream of MAPK and reduced expression of proteins involved in iodine

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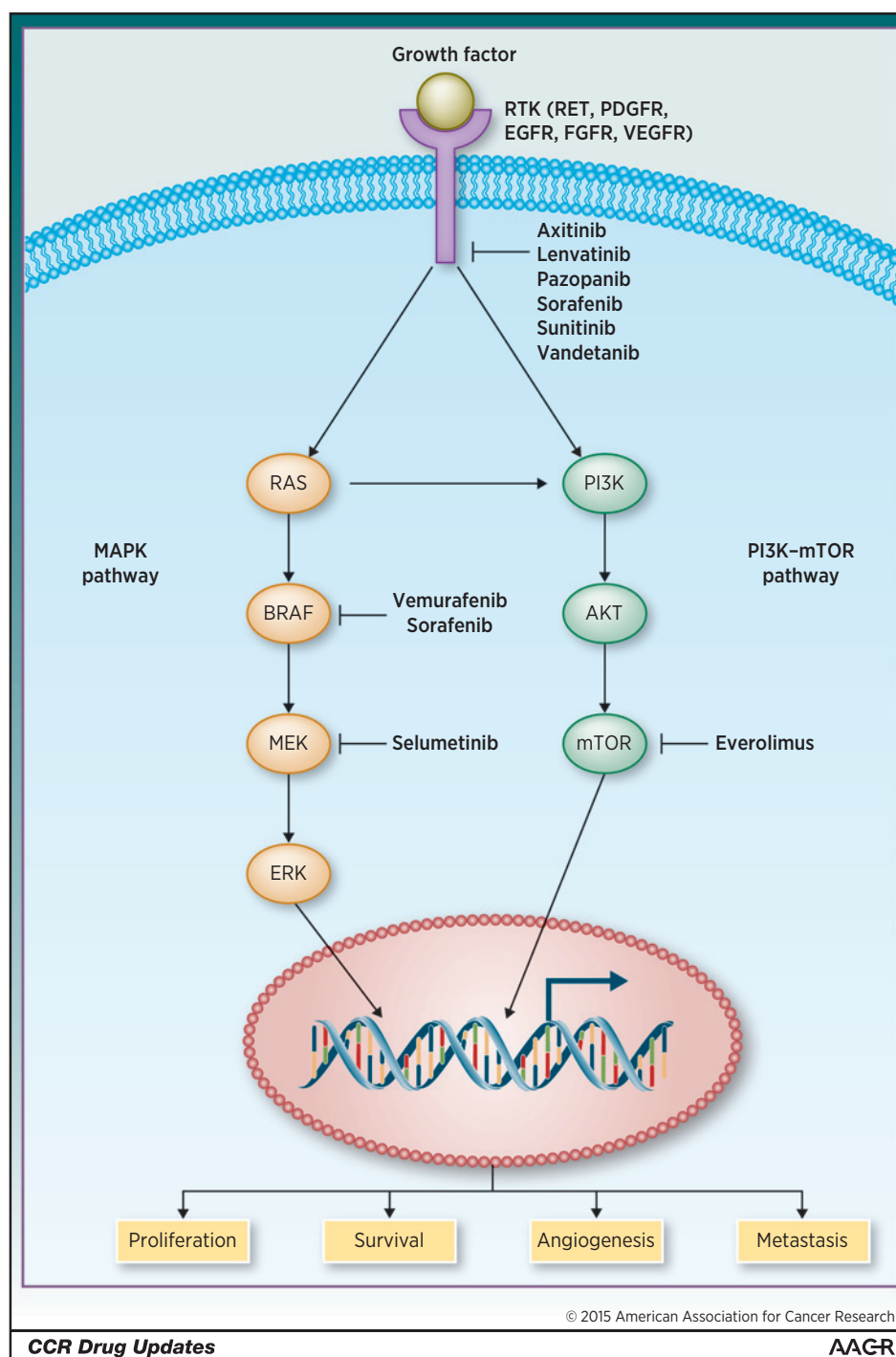
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Figure 1.

Two receptor pathways involved in pathogenesis of DTC. Activation of RTK such as RET, PDGFR, EGFR, FGFR, and VEGFR by growth factors leads to downstream effectors mainly through the MAPK (left) or PI3K-mTOR (right) signal transduction pathways to increase tumor proliferation, survival, angiogenesis, and metastasis. Selective kinase inhibitors being studied in differentiated thyroid cancer are illustrated. Lenvatinib, along with sorafenib, axitinib, pazopanib, sunitinib, and vandetanib, exert inhibitory action at the tyrosine receptor level. BRAF can be inhibited by vemurafenib and sorafenib, whereas MEK can be inhibited by selumetinib. Finally, everolimus, an mTOR inhibitor, is also being studied.



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metabolism which may explain the mechanism for high RAI resistance (2). On the other hand, the RAS-like mutation subgroups (RL-PTC) are more homogenous, enriched for highly differentiated follicular tumors, lower risk of recurrence and RAI refractoriness, and with activation of both the MAPK and PI3K-mTOR pathways.

Tumor angiogenesis also plays a key role in tumor growth, survival, and development of metastasis. VEGF binds to VEGFR which activates both the MAPK and PI3K-mTOR pathways.

Overexpression of VEGF is prevalent in DTCs and is associated with increased tumor size, extrathyroidal extension, and BRAF mutations (4, 5). It was found that VEGF may signal in an autocrine loop in DTCs and blockade of either VEGF or its receptors with neutralizing antibodies may significantly increase apoptosis in VEGFR-positive thyroid cancer cell lines (6). VEGF immunohistochemistry (IHC) was shown as a marker for metastasis spread in PTC where metastatic papillary carcinoma had a higher IHC staining than nonmetastatic papillary cancer

Table 1. Summary of therapeutic effects of various targeted therapies in patients with advanced RAI-refractory DTC

Drug	Molecular targets			Number of patients	Primary outcome	Other outcomes	Adverse events	References
	RET	VEGFR1	VEGFR2					
<i>Phase III trials</i>								
Sorafenib (Nexavar; Bayer)	X	X	X	417	PFS 10.8 vs. 5.8 months (HR, 0.59; 95% CI, 0.45–0.75; $P < 0.0001$)	PR 12.2% vs. 0.5% ($P < 0.0001$), SD 54.1% vs. 33.8% ($P < 0.0001$)	Hand-foot skin reaction (76.3%), diarrhea (68.6%), alopecia (67.1%), desquamation (50.2%)	Brose 2014 (11)
Lenvatinib (Lenvima; Eisai)	X	X	X	392 (131 placebo)	PFS 18.3 vs. 3.6 months (HR, 0.21; 99% CI, 0.14–0.31; $P < 0.001$)	CR 1.5% vs. 0%; PR 63% vs. 1.5%	Hypertension (68%), diarrhea (59%), fatigue (59%), anorexia (50%), weight loss (46%), nausea (41%)	Schlumberger 2015 (2)
<i>Phase II trials</i>								
Axitinib (Inlyta; Pfizer)	X	X	X	45	PFS 18.1 months	PR 31%, SD 42%	Hypertension (12%), fatigue (5%), proteinuria (5%)	Cohen EE, JCO 2008 (15)
Pazopanib (Votrient; Novartis)	X	X	X	37	PFS at 1 year 47%; median PFS 11.7 months	PR 49%, OS at 1 year 81%	Fatigue (74%), skin hypopigmentation (72%), diarrhea (69%), nausea (69%)	Bible 2010 (14)
Sunitinib (Sutent; Pfizer)	X	X	X	28 DTC+ 5 MTC	ORR 31% (95% CI, 16–47%) CR 3%, PR 28%, SD 46%		Fatigue (11%), neutropenia (34%), hand-foot syndrome (17%), diarrhea (17%), and leukopenia (31%)	Carr 2010 (13)
Sunitinib (Sutent)	X	X	X	31	PR 13, SD 68%, PD 10%, NE 13%		Fatigue (79%), diarrhea (56%), hand-foot syndrome (53%), neutropenia (49%), and hypertension (42%)	Cohen EE, ASCO 2008 (12)
Vandetanib (Caprelsa; AstraZeneca)	X	X	X	145 (73 placebo)	PFS 11.1 vs. 5.8 months (HR, 0.63; 60% CI, 0.54–0.74, $P = 0.008$)	ORR and OS trend higher, but not of significance	QTc elongation (14% v 0%), diarrhea (10% vs 0%), asthenia (7% vs 4%), fatigue (5% vs 0%)	Leboulleux 2012 (17)
Vemurafenib (Zelboraf; Genentech)	X	X	X	51	ORR	PFS 15.6 months in TKI naïve, PFS 6.8 months TKI treated	Rash, weight loss, fatigue, alopecia	Brose 2013 (18)
Selumetinib (AZD6244; AstraZeneca)	X	X	X	32	PR 3%, SD 54%	PFS 23 weeks	Rash (59%), diarrhea (44%), fatigue (41%), peripheral edema (31%), elevated liver enzymes (23%)	Hayes 2012 (21)
Everolimus (Afinitor; Novartis)	X	X	X	25	PR 4%, SD 76%	PFS 43 weeks	Mucositis (84%), anorexia (44%), elevated liver enzymes (26%)	Lim 2013 (22)
Everolimus + sorafenib	X	X	X	19 DTC	PR 58%, SD 37%		Hypertension (33%), rash (25.6%), hematologic abnormalities (20.5%), hyperglycemia (12.8%)	Sherman 2013 (23)

Abbreviations: CR, complete response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

($P < 0.001$; ref. 5). This was again examined in a different study which found a higher number of specific diffuse pattern of intense IHC for VEGF in patients with distant metastasis at diagnosis (63% vs. 15%, $P = 0.005$), local recurrence (58% vs. 13%, $P = 0.001$), and distant recurrence (83% vs. 14%, $P = 0.001$). Finally, intense VEGF expression was associated with significantly shorter recurrence-free survival than other staining patterns ($P = 0.007$; ref. 7).

Another angiogenic factor, the FGFR family, was also shown to be involved in thyroid cancer. FGFR-1 and -3 were expressed in most well-differentiated tumor types, whereas FGFR-4 was expressed in aggressive rapidly proliferating tumor types. Pharmacologic FGFR-4 inhibition resulted in proliferation arrest of follicular thyroid carcinoma-derived cell growth in xenograft mice (8).

Multitargeted Kinase Inhibitors

Development of oral kinase inhibitors to directly inactivate the driving tumorigenic pathways with manageable toxicity profiles has changed the treatment landscape for patients with refractory DTC. Table 1 summarizes the current clinical trials evaluating various targeted therapies for the treatment of DTC.

Sorafenib was among the first MKI to demonstrate efficacy and was approved for use in locally recurrent or metastatic progressive DTC refractory to RAI in November 2013. Sorafenib targets RET/PTC, VEGFR 1–3, and BRAF. Two phase II trials at a dose of 400 mg twice daily showed partial response (PR) rates of 15% to 23% (9, 10). Median PFS from the two studies were between 15 and 20 months (9, 10). A subsequent phase III, double-blinded, randomized controlled trial (RCT) showed improvement in the primary endpoint of median PFS of 10.8 months with sorafenib compared with 5.8 months on placebo (HR, 0.59; 95% confidence interval (CI), 0.45–0.76; ref. 11). This study included 417 patients with locally advanced or metastatic DTC progressing within the past 14 months of study entry. Subgroup analysis reported similar treatment response regardless of BRAF or RAS mutation status. Adverse events (AE) occurred in 98% of the patients with most frequent events requiring treatment which included palmar–plantar erythrodysesthesia, diarrhea, alopecia, and skin rash or desquamation. These events led to dose interruption in 66% of patients, dose reduction in 64%, and discontinuation in 18%.

Sunitinib inhibits RET/PTC subtypes 1/3 and VEGFR 1–3. It was studied in an open label phase II trial in 31 patients with progressive DTC at 50 mg daily, 4 weeks on and 2 weeks off. Preliminary reports demonstrated a PR in 13% of patients and stable disease (SD) in 68% with response duration of more than 12 weeks in 17% of patients (12). In another phase II trial using sunitinib 37.5 mg daily in 35 patients with FDG-PET avid, RAI refractory, metastatic DTC (28/35) and MTC, overall response rate (ORR) was 31% with complete response (CR) in 3% of the patients, PR in 28%, and SD in 46% (13).

Pazopanib inhibits VEGFR, FGFR, and PDGFR. In a phase II trial of 37 patients with refractory, progressive metastatic DTC, PR was achieved in 49% with pazopanib 800 mg daily (14). PFS at 1 year was 47% and the median PFS was 11.7 months. The median overall survival (OS) at 1 year was 81%. Interestingly, serum levels of pazopanib were higher in patients who obtained PR than in those who did not. Major AEs include fatigue, skin hypopigmentation, diarrhea, and nausea and 43% of patients required dose

reduction. Of note, the FDA placed a black box warning on this medication due to severe and fatal hepatotoxicity observed in renal cell carcinoma patients.

Axitinib inhibits VEGFR 1–3. In a multicenter phase II study with 45 patients with advanced or metastatic DTC, PR was achieved in 31% and SD in 38% with axitinib 5 mg twice daily (15). Median PFS was 18 months with median follow-up of 16.6 months. The most common AEs were hypertension, stomatitis, fatigue, and diarrhea. Only 13% of patients discontinued axitinib due to AEs. In a second phase II trial, the overall ORR was 35% with (18 PR) and 18 patients with stable disease for more than 16 weeks with same dose of axitinib. Median PFS was 16.1 months with median OS of 27.2 months. Most common AEs were similar—fatigue, dyspnea, diarrhea, decrease weight, pain in extremity, hypertension, decreased appetite, palmar–plantar erythrodysesthesia, hypocalcemia, and myalgia. Quality of life was maintained during treatment with axitinib without any deterioration or interference in daily life caused by symptoms (16).

Vandetanib inhibits VEGFR2, RET/PTC subtype 1 and 3, and EGFR. In a phase II trial of 145 patients with locally advanced or metastatic DTC, vandetanib 300 mg daily led to improvement in PFS from 5.8 months in placebo group to 11.1 months in vandetanib group (17). ORR and OS were higher in the vandetanib arm but did not reach statistical significance. Subgroup analysis showed those with papillary thyroid cancer had the best response, whereas those with follicular or poorly differentiated carcinoma had the worst response. The most common toxicities were QT prolongation, diarrhea, asthenia, and fatigue. A large phase III RCT is currently ongoing.

Selective BRAF Inhibitors

Vemurafenib is a selective inhibitor of BRAF V600E mutant. In a phase II trial of 51 patients with progressive RAI-refractory BRAF V600-mutant PTC, half of the enrolled patients were previously treated with antiangiogenic kinase inhibitors such as sorafenib. Preliminary results showed PR of 35% in the TKI treatment-naïve group with median PFS of 15.6 months compared with PR of 29% and PFS of 6.3 months in the group previously treated with TKI (ref. 18, NCT01286753, NO25530). AEs included rash, weight loss, fatigue, and hyperbilirubinemia.

Dabrafenib is another BRAF-specific inhibitor and was effective in 14 patients with BRAF V600E-mutant thyroid carcinoma refractory to RAI in a phase I study (19). PR achieved in 29% of patients and SD in 50%. A phase II study comparing dabrafenib versus dabrafenib plus MEK inhibitor trametinib is ongoing.

Other Targeted Therapies

Selumetinib, a selective MEK 1/2 inhibitor, was shown to have radiosensitizing activity in patients with previously RAI-refractory PTC achieving increased RAI uptake after selumetinib in a small pilot phase I study (20). In a phase II trial of 32 RAI-refractory patients administering selumetinib 100 mg twice daily, PR was achieved in 3% of patients and SD in 66% (21).

Everolimus, an inhibitor of mTOR, had poor efficacy as monotherapy in a phase II study at 10 mg daily with PR in 4% of 25 enrolled patients and PFS of 43 weeks (22). However, a second trial investigating the combination of everolimus and sorafenib is ongoing and preliminary results showed synergistic effect with PR

achieved in 58% of patients and SD in 37% when a combination of everolimus 5 mg daily and sorafenib 400 mg twice daily was given (23).

Lenvatinib

Preclinical data

Lenvatinib has *in vitro* kinase inhibitory activity strongly against VEGFR 1–3, FGFR 1–3, RET, and cKIT with half maximal inhibitory concentration (IC_{50}) of 2.3–4.7 nmol/L, 27–61 nmol/L, 12 nmol/L, and 6.4 nmol/L, respectively (24). This is in contrast to sorafenib which has weaker inhibitory activity against VEGFR 1–2 (IC_{50} = 16–21 nmol/L) and FGFRs (IC_{50} = 150–340 nmol/L). *In vitro*, lenvatinib was shown to inhibit VEGF- and FGF2-driven proliferation and tube formation of HUVECs via angiogenesis. However, lenvatinib did not show potent *in vitro* antiproliferative activity for 9 of 11 human thyroid cancer cell lines, except in the RO82-W-1 thyroid cancer cell line which highly overexpressed FGFR1. Lenvatinib was also shown to significantly inhibit the growth of KP-1/VEGF tumor cell line which was enhanced by VEGF-driven angiogenesis.

Despite the *in vitro* studies, lenvatinib showed significant antitumor activity in five DTC xenograft nude mouse models (25). This supports the notion that lenvatinib specifically targets the microvascular environment dependent on angiogenic VEGFR and FGFR signaling pathways rather than tumor proliferation pathways or cell cycle. Expectedly, antitumor activity of lenvatinib was shown to be highly associated with vascular score in a panel of 19 human tumor xenograft models consisting of different cancer types.

Clinical trials

In a phase II trial, 58 patients with advanced, RAI refractory, DTCs who had disease progression during the previous 12 months received lenvatinib 24 mg daily until disease progression, toxicity, withdrawal, or death. After more than 14 months of follow-up, ORR was 50% (95% CI, 37%–63%) with only PR but median response duration of 12.7 months. PFS was 12.6 months (95% CI, 9.9–16.1 months; ref. 26).

The promising phase II findings prompted a follow-up phase III study of lenvatinib in differentiated cancer of the thyroid (SELECT) trial (2). As a result of this pivotal study demonstrating dramatic efficacy and manageable side effects of lenvatinib compared with placebo, FDA expedited approval of lenvatinib for the treatment of patients with locally recurrent or metastatic RAI-refractory DTCs. This is the second drug approved for the patient population.

The SELECT trial was a randomized, double-blinded, placebo controlled study with 392 patients from 21 different countries with progressive refractory DTCs. These patients had proven disease progression within the previous 13 months by independent radiology review based on the RECIST v1.1 criteria, were refractory to RAI treatment, and had up to one prior antiangiogenic therapy. A majority of patients (96%) had good performance status with ECOG of 0–1 and did not have prior antiangiogenic therapies (75%). Almost all of the patients with metastatic disease had pulmonary involvement (99%). Patients were randomized in 2:1 fashion, after stratification by geographic region (Europe, North America, or other), age (≥ 65 years old or >65 years old), and prior antiangiogenic therapy, into the lenvatinib arm receiving lenvatinib 24 mg daily (261 patients) and the

placebo arm (131 patients). Crossover from placebo to open label lenvatinib was allowed based upon disease progression.

The SELECT trial met its primary endpoint of an improvement in PFS assessed on the basis of the RECIST v1.1 criteria. Median PFS improved significantly from 3.6 months in placebo group to 18.3 months in lenvatinib group with an HR of 0.21 (95% CI, 0.4–0.31; $P < 0.0001$; ref. 2). Improvement in PFS was seen in all of the predefined subgroups. ORR was seen in 64.8% patients treated with lenvatinib; 1.5% of the study subjects achieved complete response, whereas 63% achieved PR. The median time to response was 2 months (95% CI, 1.9–3.5 months). Response for lenvatinib was long lasting with 75% of responders having an objective response duration of more than 9.4 months. The median OS has not been reached. Most common grade 3 or more AEs were hypertension (42%), proteinuria (10%), weight loss (10%), and diarrhea (8%). Other less common but serious AEs include heart failure, thromboembolism, hepatic and renal failure, bowel perforation, and QT prolongation. Dose interruption was necessary in 82% of the patients, dose reduction in 67%, and discontinuation in 14%.

In a subgroup analysis, a numeric trend towards improved PFS for patients receiving lenvatinib first-line, as compared with those receiving it after a prior VEGF-targeted therapy. Sorafenib was the most commonly used prior anti-VEGF therapy (77%), then sunitinib (9%) and pazopanib (5%). Among lenvatinib-treated patients, anti-VEGF-naïve patients demonstrated a comparable PFS benefit to that of prior anti-VEGF-treated patients. In anti-VEGF-naïve patients, a median PFS of 18.7 months was seen in the lenvatinib group versus 3.6 months in placebo group. In anti-VEGF-pretreated patients, a median PFS of 15.1 months was seen in the lenvatinib group versus 3.6 months in the placebo group. The ORR was also similar between both groups, with 65.6% in the anti-VEGF-naïve patients compared with 62.1% in the anti-VEGF-treated patients. Median times-to-response were also similar with 1.9 months and 2.0 months in anti-VEGF-naïve and prior anti-VEGF-treated patients, respectively.

Biomarkers

Biomarkers have been gathering interest in early prediction of treatment efficacy, toxicities, and resistance in DTC. In particular, circulating angiogenic factors (CAF) have been under heavy investigations. Vascular damage or elevated tumor hypoxia during treatment are thought to elicit an acquired compensatory mechanism of upregulation of alternative proangiogenic factors and downregulation of angiogenic inhibitors to maintain vascular integrity. Therefore, levels of proangiogenic factors such as VEGF and stromal cell-derived factor 1 alpha (SDF1A) from tumor tissues increases in the presence of efficacious VEGF inhibition. On the contrary, level of circulating angiogenetic inhibitors such as angiopoietin-2 (ANG-2) decrease.

In a phase I study with biomarkers, in the presence of lenvatinib, proangiogenic SDF1A and VEGF levels significantly increased and correlated with treatment response (27). For the SELECT trial, blood samples were collected at baseline, cycle 1 day 15, and day 1 of subsequent cycles. VEGF level was again found to be increased and correlated with tumor shrinkage. On the other hand, levels of two inhibitory CAFs—ANG-2 and angiopoietin receptor (TIE-2)—decrease with treatment and are inversely correlated with tumor shrinkage (2). PFS HR of lenvatinib to placebo for patients with low ANG-2 (HR, 0.08; 95% CI, 0.04–0.17) was less than those with high ANG-2 (HR, 0.24; 95% CI, 0.18–0.33)

regardless of baseline CAF levels or BRAF/RAS mutational status. Finally, among lenvatinib-treated patients with disease reponse, almost all patients had a decrease in levels of ANG-2, and TIE-2 at cycle 2 compared with baseline. An increase in levels of ANG-2, and TIE-2 was observed to be an early indication for disease progression. Further analyses using these biomarkers may identify those with most likely will benefit from lenvatinib.

Circulating tumor or epithelial cells (CEC) have been implicated as prognostic biomarker in metastatic breast, prostate, and colorectal cancer (28–30). This is based on the idea that disseminated tumor cells can represent a real time reflection of tumor activity and the ability for dissemination in the body. An improved therapeutic effect of lenvatinib was correlated with the number of CECs with expression of cKIT, a factor important in survival of disseminated tumor cells in new host environment (31). In a phase I dose escalation study with 27 patients with DTCs, lenvatinib led to a significantly decreased number of cKIT (+) CECs but not cKIT(–) CECs (31). Patients with excellent response to lenvatinib had a significant change from baseline cKIT (+) CECs within 14 days suggesting that antiangiogenic activity correlated with antitumor activity in DTC.

Conclusion and Future Directions

RAI-refractory recurrent DTCs is a heterogeneous group of thyroid cancer with diverse histology, disease progression, and genomic alterations. Overall survival is usually poor for those with aggressive metastatic disease due to limited treatment options. Management of this unique group of patients is improving with better understanding of the genomic landscape of somatic aberrations and development of targeted therapies. The most recent example is the impressive result from the SELECT trial demonstrating improved ORR and PFS in subjects who received lenvatinib. The timely approval of lenvatinib now offers patients another chance at disease control and survival. Ongoing phase II or III trials using other targeted therapies will hopefully continue to expand the treatment options beyond the two currently approved drugs. At this time, there are no head-to-head comparisons between sorafenib and lenvatinib in the first-line setting.

References

- SEER Stat Fact Sheets: Thyroid Cancer [1 screen] [cited 2015 Sep 5]. Available from: <http://seer.cancer.gov/statfacts/html/thyro.html>.
- Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 2015;372:621–30.
- Xing M. Molecular pathogenesis and mechanisms of thyroid cancer. *Nat Rev Cancer* 2013;13:184–99.
- Bunone G, Vigneri P, Mariani L, Buto S, Collini P, Pilotti S, et al. Expression of angiogenesis stimulators and inhibitors in human thyroid tumors and correlation with clinical pathological features. *Am J Pathol* 1999;155:1967–76.
- Klein M, Vignaud JM, Hennequin V, Toussaint B, Bresler L, Plenat F, et al. Increased expression of the vascular endothelial growth factor is a pejorative prognosis marker in papillary thyroid carcinoma. *J Clin Endocrinol Metab* 2001;86:656–8.
- Vieira JM, Santos SC, Espadinha C, Correia I, Vag T, Casalou C, et al. Expression of vascular endothelial growth factor (VEGF) and its receptors in thyroid carcinomas of follicular origin: a potential autocrine loop. *Eur J Endocrinol* 2005;153:701–9.
- Lennard CM, Patel A, Wilson J, Reinhardt B, Tuman C, Fenton C, et al. Intensity of vascular endothelial growth factor expression is associated with increased risk of recurrence and decreased disease-free survival in papillary thyroid cancer. *Surgery* 2001;129:552–8.
- St Bernard R, Zheng L, Liu W, Winer D, Asa SL, Ezzat S. Fibroblast growth factor receptors as molecular targets in thyroid carcinoma. *Endocrinology* 2005;146:1145–53.
- Gupta-Abramson V, Troxel AB, Nellore A, Puttaswamy K, Redlinger M, Ransone K, et al. Phase II trial of sorafenib in advanced thyroid cancer. *J Clin Oncol* 2008;26:4714–9.
- Kloos RT, Ringel MD, Knopp MV, Hall NC, King M, Stevens R, et al. Phase II trial of sorafenib in metastatic thyroid cancer. *J Clin Oncol* 2009;27:1675–84.
- Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 2014;384:319–28.
- Cohen EE, Needles BM, Cullen KJ, Wong SJ, Wade JL III, Ivy SP, et al. Phase 2 study of sunitinib in refractory thyroid cancer. *J Clin Oncol (Meeting Abstracts)* 2008;26 Suppl 15:6025.
- Carr LL, Mankoff DA, Goulart BH, Eaton KD, Capell PT, Kell EM, et al. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer and metastatic medullary carcinoma of the

However, it appears that lenvatinib is quite promising with PFS of 18.3 months and HR of 0.21 compared with sorafenib which had PFS 10.8 months with HR 0.59. Toxicity profiles of the two medications are slightly different and may be the deciding factor for some patients.

Many questions remain to be addressed to optimize outcome. First, the specific subset of patients who may most benefit from treatment initiation needs to be better defined. For example, will early treatment benefit patients with asymptomatic low volume disease despite potential treatment adverse events? Development of clinical prognostication using tumor molecular signatures using next generation sequencing to differentiate those with aggressive disease may help guide these pretreatment decisions. Second, the appropriate sequence and combination of various targeted therapies to achieve superior response and survival without significant toxicity remains to be determined. As many more targeted agents actively under investigations and potential wide repertoire of available options, identification of the driver somatic alterations may guide the precise choice of therapy targeting the appropriate components of the MAPK or mTOR pathway. Biomarkers such as CEC or CAF may further predict treatment response. In summary, lenvatinib represents an important stride made against RAI-refractory DTCs. Further research in the molecular mechanisms of thyroid cancer continues to be crucial in addressing challenges of maximizing clinical benefits and limiting toxicities in these patients.

Disclosure of Potential Conflicts of Interest

E.E.W. Cohen reports receiving speakers bureau honoraria from Eisai. No potential conflicts of interest were disclosed by the other author.

Authors' Contributions

Conception and design: E.E.W. Cohen

Development of methodology: E.E.W. Cohen

Writing, review, and/or revision of the manuscript: K.T. Yeung, E.E.W. Cohen

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- thyroid with functional imaging correlation. *Clin Cancer Res* 2010;16:5260–8.
14. Bible KC, Suman VJ, Molina JR, Smallridge RC, Maples WJ, Menefee ME, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. *Lancet Oncol* 2010;11:962–72.
 15. Cohen EE, Rosen LS, Vokes EE, Kies MS, Forastiere AA, Worden FP, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. *J Clin Oncol* 2008;26:4708–13.
 16. Locati LD, Licitra L, Agate L, Ou SH, Boucher A, Jarzab B, et al. Treatment of advanced thyroid cancer with axitinib: Phase 2 study with pharmacokinetic/pharmacodynamic and quality-of-life assessments. *Cancer* 2014;120:2694–703.
 17. Leboulloux S, Bastholt L, Krause T, de la Fouchardiere C, Tennvall J, Awada A, et al. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. *Lancet Oncol* 2012;13:897–905.
 18. Brose MS, Cabanillas ME, Cohen EEW, Wirth L, Sherman S, Riehl T. An open-label, multi-center phase 2 study of the BRAF inhibitor vemurafenib in patients with metastatic or unresectable papillary thyroid cancer (PTC) positive for the BRAF V600 mutation and resistant to radioactive iodine [abstract]. In: Proceedings of the European Cancer Congress. 2013; 2013 Sep 27–Oct 1; Amsterdam, The Netherlands. Brussels (Belgium): European CanCer Organisation; 2013. Abstract LBA28.
 19. Falchook GS, Millward M, Hong D, Naing A, Piha-Paul S, Waguespack SG, et al. BRAF inhibitor dabrafenib in patients with metastatic BRAF-mutant thyroid cancer. *Thyroid* 2015;25:71–7.
 20. Ho AL, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *N Engl J Med* 2013;368:623–32.
 21. Hayes DN, Lucas AS, Tanvetyanon T, Krzyzanowska MK, Chung CH, Murphy BA, et al. Phase II efficacy and pharmacogenomic study of Selumetinib (AZD6244; ARRY-142886) in iodine-131 refractory papillary thyroid carcinoma with or without follicular elements. *Clin Cancer Res* 2012;18:2056–65.
 22. Lim SM, Chang H, Yoon MJ, Hong YK, Kim H, Chung WY, et al. A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes. *Ann Oncol* 2013;24:3089–94.
 23. Sherman EJ, Ho AL, Fury MG, Baxi SS, Haque S, Lipson BL, et al. Phase II study of everolimus and sorafenib for the treatment of metastatic thyroid cancer. *J Clin Oncol* 31, 2013 (suppl; abstr 6024).
 24. Tohyama O, Matsui J, Kodama K, Hata-Sugi N, Kimura T, Okamoto K, et al. Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. *J Thyroid Res* 2014;2014:638747.
 25. Yamamoto Y, Matsui J, Matsushima T, Obaishi H, Miyazaki K, Nakamura K, et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. *Vasc Cell* 2014;6:18.
 26. Cabanillas ME, Schlumberger M, Jarzab B, Martins RG, Pacini F, Robinson B, et al. A phase 2 trial of lenvatinib (E7080) in advanced, progressive, radioiodine-refractory, differentiated thyroid cancer: a clinical outcomes and biomarker assessment. *Cancer* 2015;121:2749–56.
 27. Koyama N, Saito K, Nishioka Y, Yusa W, Yamamoto N, Yamada Y, et al. Pharmacodynamic change in plasma angiogenic proteins: a dose-escalation phase 1 study of the multi-kinase inhibitor lenvatinib. *BMC Cancer* 2014;14:530.
 28. Cristofanilli M, Budd GT, Ellis MJ, Stopeck A, Matera J, Miller MC, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med* 2004;351:781–91.
 29. de Bono JS, Scher HI, Montgomery RB, Parker C, Miller MC, Tissing H, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res* 2008;14:6302–9.
 30. Cohen SJ, Punt CJ, Iannotti N, Saidman BH, Sabbath KD, Gabrail NY, et al. Relationship of circulating tumor cells to tumor response, progression-free survival, and overall survival in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:3213–21.
 31. Yamada K, Yamamoto N, Yamada Y, Nokihara H, Fujiwara Y, Hirata T, et al. Phase I dose-escalation study and biomarker analysis of E7080 in patients with advanced solid tumors. *Clin Cancer Res* 2011;17:2528–37.