

## New Directions With Targeted Agents in the Treatment of Advanced Thyroid Cancer

Medical writer: Aarati Ranganathan, PhD

Reviewed by: Roger Cohen, MD

Release date: December 31, 2008  
Expiration date: December 31, 2009

### 0.5 AMA PRA Category 1 Credit™

#### Target Audience

This publication is intended for medical oncologists involved in the care of patients with thyroid cancer. No specific skills or knowledge other than a basic training in oncology is required for successful participation in this activity.

#### Accreditation and Credit Designation

Physicians' Education Resource is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Physicians' Education Resource designates this educational activity for a maximum of 0.5 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

#### Overview and Purpose

Initial management of the well-differentiated and curable types of thyroid cancer involves a multimodality approach, including surgery and radiation therapy with iodine-131 (<sup>131</sup>I). However, effective therapeutic options are lacking for radioiodine-refractory or -resistant advanced disease and the aggressive types of thyroid cancers that do not respond to <sup>131</sup>I. Numerous cytotoxic regimens have failed to demonstrate significant clinical benefit. Recently, the pivotal roles of tyrosine kinases (TKs) such as Ret, B-Raf, vascular endothelial growth factor (VEGF) receptor, and epidermal growth factor receptor (EGFR) in the tumorigenesis of thyroid cancer have been identified. Chromosomal rearrangements in the *RET* proto-oncogene leading to formation of the *RET*/papillary thyroid carcinoma (PTC) oncogene or activation of the *RET* proto-oncogene through germline point mutations occur in 20%-100% of papillary and medullary thyroid cancers. Expression of VEGF and mutations in *BRAF* are correlated with poor prognosis in PTC. In preclinical thyroid cancer models, agents targeting the Ret/B-Raf, VEGF, and EGFR pathways have demonstrated significant antitumor effects. In patients with advanced thyroid cancers, inhibition of these key signaling molecules with novel multitargeted and anti-EGFR TK inhibitors (TKIs) holds therapeutic potential.

The purpose of this activity is to summarize the rationale for investigating and recent clinical data on multitargeted TKIs in advanced thyroid cancer.

#### Learning Objectives

Upon completion of this educational activity, you should be able to:

- Discuss the rationale for targeting angiogenesis and the growth factor signaling pathways in thyroid cancer
- Compare the efficacies of novel multitargeted and anti-EGFR TKIs in advanced thyroid cancer
- Assess the safety and tolerability of multitargeted TKIs in early-phase trials of advanced thyroid cancer

### Introduction

Thyroid cancer arises from either follicular cells or parafollicular cells (C cells) (Table 1).<sup>1</sup> Follicular thyroid malignancies include well- and intermediately differentiated thyroid cancers (DTCs); comprising papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and Hürthle cell thyroid cancer (HCTC) subtypes; and undifferentiated anaplastic thyroid cancer (ATC).<sup>2</sup> Parafollicular cells give rise to medullary thyroid cancer (MTC). The DTCs account for the majority of thyroid cancers and are generally curable, while ATC is less common but more aggressive. Medullary thyroid cancer, which is classified as either familial or sporadic, is an uncommon type of cancer.<sup>2,3</sup>

The initial treatment for DTC is surgery and iodine-131 (<sup>131</sup>I), and most patients are cured of their disease. For advanced DTC that is not amenable to curative surgery, <sup>131</sup>I is the primary treatment, yielding a 5-year overall survival (OS) rate of approximately 50% that is maintained at 10 years.<sup>2,4</sup> No effective treatment is available for <sup>131</sup>I-refractory or -resistant disease, and the long-term OS rate is low. In a study in 444 patients with incurable metastatic DTC, the 10-year OS rate in the patients responding to <sup>131</sup>I was 92% compared to only 29% in those with <sup>131</sup>I-refractory disease and 10% in those with <sup>131</sup>I-resistant disease.<sup>4</sup> Chemotherapeutic drugs, such as doxorubicin, platinum agents, and taxanes, have had variable clinical benefit in this disease setting.<sup>5,6</sup> In most studies, objective response rates (RRs) with doxorubicin were no better than 30%-40%, and responses were not durable.<sup>6</sup> Multimodality approaches to treatment, including surgery, radiation therapy, and chemotherapy, have also been attempted in patients with advanced incurable MTC and in those with ATC with minimal benefit.<sup>2</sup>

Increased understanding of the molecular pathogenesis of the different subtypes of thyroid cancer has led to the investigation of a number of molecular-targeted agents as treatment for advanced disease.<sup>7-17</sup>

### Rationale for Molecular-Targeted Therapy in Advanced Thyroid Cancer Angiogenesis

Increased expression of proangiogenic vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFRs) has been noted in patients with DTC compared to controls and correlates with larger primary tumor size in younger patients.<sup>18</sup> Intensity of VEGF expression is associated with higher local and

distant recurrence rates and shorter recurrence-free survival in PTC.<sup>19</sup> Serum VEGF levels correlate with clinical disease status in DTC.<sup>20</sup> In preclinical studies, an anti-VEGF monoclonal antibody demonstrated significant in vivo inhibition of PTC and ATC growth.<sup>21,22</sup> Blocking VEGFR signaling with a tyrosine kinase inhibitor (TKI) has yielded antiangiogenic effects and improvement in survival in an orthotopic mouse model.<sup>23</sup>

### Ret, Ras, and B-Raf Pathways

Constitutive activation of signaling via the mitogen-activated protein kinase pathway resulting from nonoverlapping genetic aberrations in the TK Ret, the guanosine 5'-triphosphate-binding protein Ras, and the serine-threonine kinase B-Raf occurs in > 70% of PTCs.<sup>24</sup> Chromosomal rearrangements in the *RET* proto-oncogene occur in approximately 20% of the adult patients with PTC. Oncogenic activation of *RET* through germline point mutations occurs in close to 100% of the patients with familial MTC and approximately 50% of those with sporadic MTC. The *BRAF* V600E mutation is found in 45% of the patients with PTC and 20% of those with ATC. The *BRAF* mutation significantly and independently correlates with poor prognosis in patients with PTC.<sup>24,25</sup> *RAS* gene mutations are rare in PTC (approximately 10%) but account for 40%-50% of the molecular subtypes of FTC and 55% of ATCs.<sup>24</sup>

Preclinical studies suggest that therapy targeting VEGF, Ret, B-Raf, and epidermal growth factor receptor (EGFR) has significant therapeutic potential for patients with thyroid cancer. Sorafenib targets VEGFR, B-Raf, Ret, platelet-derived growth factor receptor (PDGFR), and c-Kit; motesanib (AMG 706) targets VEGFR, Ret, PDGFR, and c-Kit; axitinib (AG-013736) targets VEGFR, PDGFR, and c-Kit;

Subtype	Percentage of Thyroid Cancers	Differentiation	Cellular Origin
Papillary	80%-85%	Well	Follicular
Follicular	10%-15%	Well	Follicular
Hürthle	3%-5%	Intermediate	Follicular
Medullary	5%-9%	Intermediate	Parafollicular/C cell
Anaplastic	1%-2%	Poor	Follicular

Dr. Ranganathan has no relevant relationships to disclose.

Dr. Cohen receives research funding from AstraZeneca, Bayer Pharmaceuticals Corporation, Novartis Pharmaceuticals Corporation, and Pfizer Inc. and is a member of the Speaker's Bureau of Bristol-Myers Squibb Company/ImClone Systems Incorporated.

This article includes discussion of investigational and/or unlabeled uses of drugs, including the use of sorafenib, axitinib (AG-013736), motesanib (AMG 706), vandetanib, gefitinib, and XL184 in thyroid cancer.

This activity is supported by an educational grant from Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals, Inc.

	VEGFR	Ret	B-Raf	EGFR	PDGFR-β/ c-Kit
Sorafenib	20-90 nM	47 nM	22 nM	NA	57 nM/68 nM
Axitinib	0.25-1.2 nM	NA	NA	NA	2.5 nM/1.7 nM
Motesanib	2-6 nM	59 nM	NA	NA	84 nM/8 nM
Vandetanib	40-1600 nM	130 nM	NA	500 nM	NA

Abbreviations: EGFR = epidermal growth factor receptor; NA = not applicable; PDGFR = platelet-derived growth factor receptor; VEGFR = vascular endothelial growth factor receptor

vandetanib targets VEGFR, Ret, and EGFR; and gefitinib targets EGFR (Table 2).<sup>5</sup> Multitargeted TKIs, including vandetanib, sorafenib, and motesanib, have inhibited Ret kinase and tumor growth in preclinical models of PTC and MTC. Sorafenib also inhibits B-Raf and has shown antitumor activity against B-Raf<sup>+</sup>ATC cell lines and xenograft models.<sup>26</sup>

## Recent Data on TKIs in Advanced Thyroid Cancer

### Sorafenib

Results from 2 phase II trials of sorafenib 400 mg b.i.d. in patients with <sup>131</sup>I-refractory metastatic thyroid cancer were reported recently. Of the 30 patients treated in a trial conducted by Dr. Gupta-Abramson and colleagues, 18 had PTC, 9 had FTC/HCTC, 1 had MTC, and 2 had poorly differentiated thyroid cancer/ATC.<sup>7</sup> Seven patients (23%) achieved a partial response (PR), and 16 (53%) had stable disease (SD) (Table 3). Median progression-free survival (PFS) was 18.2 months in all 30 patients and 19.3 months in those with DTC. Serial serum thyroglobulin (Tg) levels decreased dramatically (mean decrease: 70% within 4 months of starting therapy) in 17 of the 19 evaluable patients. Of the 9 patients who discontinued sorafenib, 6 withdrew due to adverse events (AEs). Toxicity-related dose reductions and dose interruptions occurred in 14 (47%) and 19 (63%) patients, respectively. Grade 3/4 AEs included hypertension, rash, palmar-plantar erythema, diarrhea, and elevated liver function tests (Table 4). Increases in thyroid-stimulating hormone (TSH) levels ≥ 0.10 mU/L were observed in 10 (33%) of the 30 treated patients.

In the MATISSE trial, 16 patients with DTC and 13 patients with MTC received sorafenib; 3 patients (10%) discontinued the drug, and 19 (65%) required dose reductions.<sup>8</sup> Grade 3 AEs included hypertension, hand-foot syndrome (HFS) and other skin-related events, fatigue, arthralgia, muscle cramps, and drug hypersensitivity. Severe AEs were observed in 7 patients (grade 3 hypocalcemia and colitis and grade 4 neutropenic fever: n = 1 each; infection with nonneutropenic fever: n = 4). When radiologic responses were recorded at 3, 6, and 9 months, 84%, 94%, and 100% of the patients, respectively, had SD. At 3 months, 12% of the patients had achieved a PR.

A pilot study evaluated sorafenib in patients with advanced MTC and elevated serum calcitonin (CTN) levels.<sup>9</sup> Each of the 5 patients experienced a decrease in serum CTN levels > 50% from baseline (> 90%: n = 2) following 2-3 months of therapy. An objective response was noted in 2 patients (1 complete response and 1 PR) after 6 months. Three patients experienced a marked increase in TSH levels, and all of the patients required dose reductions of 50% due to AEs.

### Axitinib

A phase II trial evaluated axitinib 5 mg b.i.d. in 60 patients with advanced thyroid cancer that was either refractory to or unsuitable for further <sup>131</sup>I therapy.<sup>10</sup> Patients with all histologies were enrolled (PTC: n = 30; FTC/HCTC: n = 15; MTC: n = 11; ATC and other histologies: n = 2 each). Eighteen patients (30%) achieved a PR, 13 (72%) of whom had not progressed at the time of analysis. An additional 23 patients (38%) had SD. Objective responses were noted among all histologies (PTC: n = 8; FTC/HCTC: n = 6; MTC: n = 2; ATC and other histologies: n = 1 each). At a median follow-up of 16.6 months, median PFS was 18.1 months, and median OS had not been reached. Levels of the tumor markers CTN and Tg were monitored; however, no correlation could be made between the biomarkers and response due to the small number of patients who were analyzed.

	Histologic Subtypes Studied	Partial Response	Stable Disease	Median Progression-Free Survival	Serum Tg Decrease ≥ 50% From Baseline
Sorafenib <sup>7</sup>	All histologies	7/30 (23%)	16/30 (53%)	18.2 months	17/19
Sorafenib <sup>8</sup>	DTC, MTC	Radiologic: 12% at 3 months	Radiologic: 84% at 3 months	NR	NR
Axitinib <sup>10*</sup>	All histologies	18/60 (30%)	23/60 (38%)	18.1 months	NR
Motesanib <sup>11</sup>	DTC	13/93 (14%)	62/93 (67%)	Estimated 9.2 months	34/75 (45%)
Motesanib <sup>5,12†</sup>	MTC	2%	47%	NR	NR
Vandetanib <sup>13</sup>	Hereditary MTC	5/30 (17%)	22/30 (73%)	NR	NR
Vandetanib <sup>14</sup>	Hereditary MTC	3/19 (16%)	12/19 (63%)	NR	NR
XL184 <sup>15</sup>	MTC	9/17 (53%)	8/17 (47%)	NR	NR
Sunitinib <sup>16</sup>	DTC	6/35 (17%)	26/35 (74%)	NR	NR
Gefitinib <sup>17*</sup>	All histologies	0/25	48% at 3 months	3.7 months	5/15 (33%)

\* Median overall survival: axitinib not reached; gefitinib 17.5 months

† n = 91

Abbreviations: DTC = differentiated thyroid cancer; MTC = medullary thyroid cancer; NR = not reported; Tg = thyroglobulin

	Number of Patients	Fatigue	Diarrhea	Weight Loss	Hypertension	Rash/PPE
Sorafenib <sup>7</sup>	30	3%	7%	10%	13%	10%/10%
Axitinib <sup>10</sup>	60	5%	3%	3%	12%	0/0
Motesanib <sup>11*</sup>	93	4%	13%	5%	25%	NR
Vandetanib <sup>13*</sup>	30	7%	10%	NR	NR	3%/NR
XL184 <sup>15*</sup>	61	2%	2%	NR	2%	2%

\* Grade 3 only

Abbreviations: NR = not reported; PPE = palmar-plantar erythema

A total of 32 patients discontinued axitinib therapy; 8 discontinuations (13%) were related to AEs, and 23 patients (38%) required toxicity-related dose reductions. The most common treatment-related AEs included fatigue (50%), diarrhea (48%), hypertension (28%), HFS (15%), and rash (15%). Grade ≥ 3 AEs included hypertension (12%), proteinuria (5%), and fatigue (5%).

### Motesanib

The clinical benefit derived from motesanib was investigated in a phase II trial in 93 patients with advanced, progressive <sup>131</sup>I-resistant DTC (PTC: n = 57; HCTC: n = 17; FTC: n = 15; other histologies: n = 4).<sup>11</sup> Motesanib 125 mg/day was given for ≤ 48 weeks. Thirteen patients (14%) achieved a PR, and 62 (67%) had SD (≥ 24 weeks: 33 [35%]). Estimated median PFS was 9.2 months. No difference in response based on histology or *BRAF* mutation status was noted. Serum Tg concentrations decreased ≥ 50% from baseline in 34 (45%) of the 75 evaluable patients; the decreases significantly correlated with radiographic response to motesanib (*P* < .001). In 11 (15%) of the 75 patients, the decrease was sustained for ≥ 24 weeks.

Treatment was discontinued in 12 (13%) of the 93 patients due to AEs. Two deaths resulted from hemorrhage. Grade 1/2 hypothyroidism, increased TSH, or both were observed in 20 patients (22%); grade ≤ 3 gallbladder toxicities in 12 patients (13%), including 5 with grade 2/3 cholecystitis; and grade 2 cardiac events in 2 patients (2%). Grade 3 AEs occurred in 51 patients (55%), and grade 4 AEs occurred in 5 patients (5%). Grade 3/4 hypertension was seen in 23 patients (25%).

Benefit from motesanib monotherapy was analyzed in a parallel cohort of 91 patients with advanced progressive MTC.<sup>5,12</sup> Two percent of the patients achieved a PR, and 47% had SD lasting ≥ 24 weeks.

## Vandetanib

Vandetanib has been assessed in patients with advanced hereditary MTC in 2 phase II trials. In a trial of vandetanib 300 mg/day, 5 (17%) of the 30 patients achieved a PR, and 22 (73%) had SD.<sup>13</sup> In 15 patients (50%), SD lasted  $\geq 24$  weeks. Serum CTN and carcinoembryonic antigen levels decreased  $\geq 50\%$  from baseline for  $\geq 4$  weeks in 23 and 15 patients, respectively. Seven patients (23%) discontinued treatment due to AEs, and 21 (70%) required dose reductions or interruptions. Grade 3 AEs included prolongation of QTc interval (n = 5), diarrhea (n = 3), and nausea (n = 3). One patient experienced grade 4 azotemia.

In a phase II trial, 19 patients received vandetanib 100 mg/day (300 mg/day if they had radiographic disease progression).<sup>14</sup> At the time of analysis, 11 patients were continuing treatment with vandetanib 100 mg/day, 4 had switched to 300 mg/day, and 3 had discontinued vandetanib due to AEs. The disease control rate (PR + SD) was 79% (PR: 3 patients [16%]; SD: 12 patients [63%]; SD  $\geq 24$  weeks: 10 patients [53%]). The most common AEs were diarrhea (n = 9), fatigue (n = 8), and rash (n = 5). Grade 3 AEs included hypertension, myalgia, and asymptomatic QTc prolongation. One patient experienced grade 4 diabetes insipidus.

## XL184

XL184 is an oral TKI that is active against Ret, VEGFR-2, and c-Met. A phase I trial of XL184 in patients with advanced cancer that was not treatable with standard regimens included an expansion at the maximum tolerated dose of 175 mg/day for additional patients with MTC, for a total of 22 patients with MTC.<sup>15</sup> Of the 17 patients with measurable disease, 9 (53%) achieved a PR. No grade 4 AEs were reported; the most common grade 3 toxicity was increased liver enzymes (n = 4). Other grade 3 AEs included diarrhea, nausea, and hypertension in 1 patient each. A phase III trial comparing XL184 to placebo in patients with locally advanced/metastatic MTC is ongoing.<sup>27</sup>

## Conclusion

An expanded understanding of the biology of thyroid cancer and the development of molecular-targeted agents inhibiting angiogenesis and other oncogenic signaling pathways raises the potential of increasing the repertoire of treatment options for patients with the disease. Early-phase trials of multitargeted TKIs have demonstrated anti-tumor RRs of 14%-53% and SD rates of 38%-74% in previously treated, advanced, incurable thyroid cancer. Further investigation to determine the role of various targeted agents in thyroid cancer is being carried out, and multiple trials assessing multitargeted TKIs in different subtypes of advanced thyroid cancer are ongoing.

Please send me future issues of Oncology Briefings

Name \_\_\_\_\_

Address \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

Fax \_\_\_\_\_

**BUSINESS REPLY MAIL**

FIRST-CLASS MAIL PERMIT NO. 2744 DALLAS TX

POSTAGE WILL BE PAID BY ADDRESSEE

## PHYSICIANS' EDUCATION RESOURCE

3500 MAPLE AVE STE 700  
DALLAS TX 75219-3902



ing. Future challenges include determining if there is cross-resistance between the different agents or if they can be administered sequentially upon disease progression or toxicity. Furthermore, identification of molecular and/or clinical markers to predict response would aid in optimizing treatment for patients with advanced thyroid cancer.

## References

- Carling T, Udelsman R. Cancer of the endocrine system. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman and Rosenberg's Cancer: Principles & Practice of Oncology*, 8th ed. Philadelphia, PA: Lippincott, Williams & Wilkins, 2008; 1670-80.
- Deshpande HA, Gettinger SN, Sosa JA. Novel chemotherapy options for advanced thyroid tumors: small molecules offer great hope. *Curr Opin Oncol* 2008; 20:19-24.
- Fagin J. Molecular insights into thyroid cancer. Paper presented at: Third Annual Multidisciplinary Symposium on Head and Neck Cancer; December 1, 2007; Philadelphia, PA.
- Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab* 2006; 91:2892-9.
- Sherman SI. Early clinical studies of novel therapies for thyroid cancers. *Endocrinol Metab Clin North Am* 2008; 37:511-24.
- Haugen BR. Management of the patient with progressive radioiodine non-responsive disease. *Semin Surg Oncol* 1999; 16:34-41.
- Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II trial of sorafenib in advanced thyroid cancer. *J Clin Oncol* 2008; 26:4714-9.
- Ahmed M, Barbachano Y, Riddell AM, et al. An open labelled phase 2 study evaluating the safety and efficacy of sorafenib in metastatic advanced thyroid cancer. *Ann Oncol* 2008; 19(suppl 8):218 (abstract 691PD).
- Kober F, Hermann M, Handler A, et al. Effect of sorafenib in symptomatic metastatic medullary thyroid cancer. *J Clin Oncol* 2007; 25(suppl):617s (abstract 14065). Available at: <http://www.asco.org>. Accessed: December 3, 2008.
- Cohen EEW, Rosen LS, Vokes EE, 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.
- Sherman SI, Wirth LJ, Droz J-P, et al. Motesanib diphosphate in progressive differentiated thyroid cancer. *N Engl J Med* 2008; 359:31-42.
- Schlumberger MJ, Elisei R, Sherman SI, et al. Phase 2 trial of motesanib diphosphate (AMG 706) in patients with medullary thyroid cancer (MTC). Paper presented at: 89th Annual Meeting of the Endocrine Society; June 2-5, 2007; Toronto, Ontario, Canada.
- Wells SA Jr, Gosnell JE, Gagel RF, et al. Vandetanib in metastatic hereditary medullary thyroid cancer: follow-up results of an open-label phase II trial. *J Clin Oncol* 2007; 25(suppl):303s (abstract 6018).
- Haddad RI, Krebs AD, Vasselli J, et al. Phase II open-label study of vandetanib in patients with locally advanced or metastatic hereditary medullary thyroid cancer. *J Clin Oncol* 2008; 26(suppl):322s (abstract 6024).
- Salgia R, Sherman S, Hong DS, et al. A phase I study of XL184, a RET, VEGFR2, and MET kinase inhibitor, in patients (pts) with advanced malignancies, including pts with medullary thyroid cancer (MTC). *J Clin Oncol* 2008; 26(suppl):158s (abstract 3522).
- Cohen E. Advances in targeted agents for thyroid cancer. Paper presented at: Fourth Annual Multidisciplinary Symposium on Head and Neck Cancer; December 6, 2008; Philadelphia, PA.
- Pennell NA, Daniels GH, Haddad RI, et al. A phase II study of gefitinib in patients with advanced thyroid cancer. *Thyroid* 2008; 18:317-23.
- Fenton C, Patel A, Dinauer C, et al. The expression of vascular endothelial growth factor and the type 1 vascular endothelial growth factor receptor correlate with the size of papillary thyroid carcinoma in children and young adults. *Thyroid* 2000; 10:349-57.
- Lennard CM, Patel A, Wilson J, 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.
- Turtle RM, Fleisher M, Francis GL, et al. Serum vascular endothelial growth factor levels are elevated in metastatic differentiated thyroid cancer but not increased by short-term TSH stimulation. *J Clin Endocrinol Metab* 2002; 87:1737-42.
- Bauer AJ, Patel A, Terrell R, et al. Systemic administration of vascular endothelial growth factor monoclonal antibody reduces the growth of papillary thyroid carcinoma in a nude mouse model. *Ann Clin Lab Sci* 2003; 33:192-9.
- Bauer AJ, Terrell R, Doniparthi NK, et al. Vascular endothelial growth factor monoclonal antibody inhibits growth of anaplastic thyroid cancer xenografts in nude mice. *Thyroid* 2002; 12:953-61.
- Kim S, Yazici YD, Calzada G, et al. Sorafenib inhibits the angiogenesis and growth of orthotopic anaplastic thyroid carcinoma xenografts in nude mice. *Mol Cancer Ther* 2007; 6:1785-92.
- Nikiforov YE. Thyroid carcinoma: molecular pathways and therapeutic targets. *Mod Pathol* 2008; 21:337-43.
- Xing M, Westra WH, Tufano RP, et al. BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer. *J Clin Endocrinol Metab* 2005; 90:6373-9.
- Salvatore G, De Falco V, Salerno P, et al. BRAF is a therapeutic target in aggressive thyroid carcinoma. *Clin Cancer Res* 2006; 12:1623-9.
- Phase 3 efficacy study of XL184 in adults with medullary thyroid cancer. ClinicalTrials.gov [Web site]. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00704730>. Accessed: December 3, 2008.

NO POSTAGE  
NECESSARY  
IF MAILED  
IN THE  
UNITED STATES

**CME Answer Card**  
Oncology Briefings  
December 2008 • Volume 6, Number 9

(Last) \_\_\_\_\_ (First) \_\_\_\_\_

Name \_\_\_\_\_

Credentials  MD  RN  PharmD  Other \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip \_\_\_\_\_

Tel ( ) \_\_\_\_\_ Fax ( ) \_\_\_\_\_

Birth Date (MM/DD) \_\_\_\_\_

E-mail (required) \_\_\_\_\_

Mark the correct answers.

- |    |                       |                       |                       |                       |                       |
|----|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|    | <b>a</b>              | <b>b</b>              | <b>c</b>              | <b>d</b>              | <b>e</b>              |
| 1. | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |                       |
| 2. | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |                       |
| 3. | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

Fax: (214) 367-3304  
Phone: (214) 367-3400

Actual time spent to complete this activity \_\_\_\_\_

**Evaluation Questions**

Please rate this CME exercise according to the scale below:  
a = excellent  
b = very good  
c = satisfactory  
d = inadequate

- How would you rate the effectiveness of this activity in meeting its stated objectives?
- How would you rate this information in enhancing your professional effectiveness in managing thyroid cancer?
- How would you rate the timeliness of content?
- Please rate the freedom from promotional or commercial bias in this activity.

- |    |                       |                       |                       |                       |
|----|-----------------------|-----------------------|-----------------------|-----------------------|
|    | <b>a</b>              | <b>b</b>              | <b>c</b>              | <b>d</b>              |
| 1. | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 2. | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 3. | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 4. | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

**INSTRUCTIONS FOR PARTICIPATION IN PRINT ACTIVITY**

To participate in this activity online, go to [www.CancerLearning.com](http://www.CancerLearning.com).

This educational activity provides a maximum of 0.5 AMA PRA Category 1 Credit.

- Read the printed material contained in this educational activity.
- Record your answers to the CME test and evaluation on the Business Reply Card.
- Indicate time spent completing this activity on the Business Reply Card. You will be awarded a certificate for the actual time spent up to the maximum number of credits designated.
- Return the Business Reply Card by December 31, 2009.
- After successful completion of the test, you will receive your certificate by e-mail. Please allow 4-8 weeks for processing.

CME credit will be granted for only 1 form of participation, either online or via the printed publication.

**CME Questions (Mark the Correct Answers)\***

- Which of the following statements has NOT been reported in preclinical studies of thyroid cancer as a rationale for therapeutic targeting of vascular endothelial growth factor (VEGF) or growth factor receptor signaling pathways?
  - Intensity of VEGF expression correlates with shorter recurrence-free survival in papillary thyroid cancer (PTC).
  - RAS mutations occur in 40%-50% of PTCs and anaplastic thyroid cancers.
  - Chromosomal rearrangements in the RET proto-oncogene occur in approximately 20% of the adult patients with PTCs.
  - Blocking VEGF receptor signaling with a tyrosine kinase inhibitor (TKI) improved survival in an orthotopic mouse model.
- Which of the following efficacy results was reported in phase II trials of multitargeted and anti-epidermal growth factor receptor TKIs in previously treated advanced thyroid cancer?
  - No objective responses were noted with sorafenib monotherapy.
  - Serum thyroglobulin levels decreased dramatically and correlated with response in the patients receiving axitinib (AG-013736).
  - Approximately 25% of the patients treated with XL184 achieved a response; all of the responders had PTC.
  - No difference in response based on histology or BRAF mutation status was noted with motesanib (AMG 706) in patients with advanced, progressive iodine-131-resistant differentiated thyroid cancers.
- Which of the following grade  $\geq 3$  adverse events was NOT noted in phase II trials of multitargeted TKIs in advanced thyroid cancer?
  - Asymptomatic QTc prolongation
  - Hypertension
  - Hypothyroidism
  - Fatigue
  - Diarrhea

\* Successful completion is determined by a score of 67% or greater.



**PHYSICIANS' EDUCATION RESOURCE**  
Advancing Cancer Care Through  
Professional Education

©Copyright 2008 by Physicians' Education Resource.  
No material may be reproduced in whole or in part, in any form, without  
written permission from the publisher.  
ISSN: 1545-1739

**Oncology Briefings**

Physicians' Education Resource  
3500 Maple Ave.  
Suite 700  
Dallas, TX 75219