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ORIGINAL ARTICLE

Motesanib Diphosphate in Progressive Differentiated Thyroid Cancer

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ABSTRACT

BACKGROUND

The expression of vascular endothelial growth factor (VEGF) is characteristic of differentiated thyroid cancer and is associated with aggressive tumor behavior and a poor clinical outcome. Motesanib diphosphate (AMG 706) is a novel oral inhibitor of VEGF receptors, platelet-derived growth-factor receptor, and KIT.

METHODS

In an open-label, single-group, phase 2 study, we treated 93 patients who had progressive, locally advanced or metastatic, radioiodine-resistant differentiated thyroid cancer with 125 mg of motesanib diphosphate, administered orally once daily. The primary end point was an objective response as assessed by an independent radiographic review. Additional end points included the duration of the response, progression-free survival, safety, and changes in serum thyroglobulin concentration.

RESULTS

Of the 93 patients, 57 (61%) had papillary thyroid carcinoma. The objective response rate was 14%. Stable disease was achieved in 67% of the patients, and stable disease was maintained for 24 weeks or longer in 35%; 8% had progressive disease as the best response. The Kaplan–Meier estimate of the median duration of the response was 32 weeks (the lower limit of the 95% confidence interval [CI] was 24; the upper limit could not be estimated because of an insufficient number of events); the estimate of median progression-free survival was 40 weeks (95% CI, 32 to 50). Among the 75 patients in whom thyroglobulin analysis was performed, 81% had decreased serum thyroglobulin concentrations during treatment, as compared with baseline levels. The most common treatment-related adverse events were diarrhea (in 59% of the patients), hypertension (56%), fatigue (46%), and weight loss (40%).

CONCLUSIONS

Motesanib diphosphate can induce partial responses in patients with advanced or metastatic differentiated thyroid cancer that is progressive. (ClinicalTrials.gov number, NCT00121628.)

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*Additional investigators who participated in this study are listed in the Appendix.

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Thyroid cancers are classified histologically into four groups: papillary, follicular, medullary, and undifferentiated or anaplastic thyroid carcinomas.[1] Papillary and follicular carcinomas (including the Hürthle-cell variant) are collectively known as differentiated thyroid cancers,[1,2] and they account for approximately 95% of incident cases.[3] Initial treatment typically involves total thyroidectomy followed by long-term administration of levothyroxine at doses that suppress thyrotropin; adjuvant radioiodine (^{131}I) is often administered as well.[2-4] This regimen is usually effective, but the 10-year recurrence rate is 20 to 30% among patients who are older, among patients with tumors larger than 4 cm in diameter, and among patients in whom the tumor extends beyond the thyroid or in whom extensive lymph-node metastases develop.[4] There is no effective treatment for radioiodine-resistant metastatic disease; the 10-year survival rate in these cases is less than 15%.[5]

Increased expression of vascular endothelial growth factor (VEGF), a potent angiogenesis stimulator, is characteristic of differentiated thyroid cancers[6,7] and is associated with increased growth, progression, and invasiveness of the tumor and with decreased recurrence-free survival.[4,8-10] For this reason, an inhibitor of angiogenesis may be effective when initial therapy fails.[11] Motesanib diphosphate (Amgen) is an oral inhibitor of the tyrosine kinases of VEGF receptors 1, 2, and 3; platelet-derived growth-factor receptor; and KIT.[12] In a phase 1 study, treatment with 125 mg of motesanib diphosphate once daily resulted in antitumor activity in patients with advanced solid cancers, including five patients with differentiated thyroid cancer.[13] In the present study, we investigated the efficacy and tolerability of motesanib diphosphate in progressive, locally advanced or metastatic differentiated thyroid cancer.

Methods

Patients

We included in the study adults who had histologically confirmed, locally advanced or metastatic differentiated thyroid cancer and documented evidence of disease progression (based on two sets of radiographic images) according to the Response Evaluation Criteria in Solid Tumors (RECIST),[14] as assessed by the investigator, within 6 months before entry into the study. A rising serum thyroglobulin level alone was not sufficient evidence of disease progression before enrollment. Other key inclusion criteria were the presence of at least one lesion that was defined as measurable according to the RECIST guidelines and that was not amenable to surgical resection or external-beam radiation therapy or was refractory to radioiodine; the absence of untreated brain metastases; an Eastern Cooperative Oncology Group performance status score of 0 to 2; and adequate hepatic, renal, and cardiac function. Patients were ineligible if they had ever received treatment with VEGF-receptor inhibitors or if they had received nonhormonal anticancer therapy within 30 days before the start of the study. The protocol was approved by each center's independent ethics committee or institutional review board, and all patients provided written informed consent before enrollment.

Study Design and End Points

This phase 2, open-label study involving a cohort of patients with differentiated thyroid cancer was conducted at 42 centers in 10 countries. A parallel cohort included similar patients with metastatic medullary thyroid cancer; data from this cohort were not included in the analysis reported here. The primary end point was an objective response according to RECIST, as assessed by a centralized, independent review. Additional end points included the duration of response, progression-free survival, the time to response, and overall survival; adverse events; pharmacokinetic characteristics; and changes in the serum thyroglobulin concentration.

Patients received 125 mg of motesanib diphosphate orally once daily for up to 48 weeks or until there was evidence of unacceptable toxicity or disease progression. Treatment was offered beyond 48 weeks in an extension study if a clinical benefit was observed. Therapy was withheld if a treatment-related grade 3 adverse event that could not be controlled with supportive care, any related grade 4 adverse event, or symptomatic hypertension occurred. Treatment could be resumed at a dose of 100 mg per day, if toxicity was reduced to a grade of 1 or less for nonhematologic toxicity or to a grade of 2 or less for hematologic toxicity, or at a dose of 75 mg per day after a second interruption of treatment that was related to toxicity.

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Adverse events were classified according to the Medical Dictionary for Regulatory Activities, and severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Patients had regular assessments of blood pressure (weekly until week 6, then every other week until week 16, and every 4 weeks thereafter), blood chemical profiles, blood counts, and urine protein levels. Free thyroxine and thyrotropin levels were measured at baseline and monthly thereafter.

ASSESSMENT OF TUMOR RESPONSE

Computed tomographic or magnetic resonance imaging scans of the neck, chest, and abdomen were obtained at 8-week intervals and when progression of the disease was suspected. An objective response (complete or partial response according to RECIST) was assessed by a centralized, independent review, with confirmation by repeat imaging studies at least 4 weeks later. A bone scintigram that showed no new osseous metastases (as compared with the findings at study entry) was also required to define an objective response in patients with follicular or Hürthle-cell carcinoma. The designation of stable disease required a single assessment of either stable disease or an unconfirmed objective response 47 days or more after the first administration of the drug.

PHARMACOKINETICS

Plasma samples to assess pharmacokinetics were collected from nine patients 15 minutes, 30 minutes, and 1, 2, 4, 6, 8, and 24 hours after the administration of the drug on day 1 of the study. To assess trough concentrations of motesanib after long-term administration, plasma was collected before the daily dose at 4-week intervals during the first 24 weeks of the study. Plasma motesanib concentrations were measured by means of liquid chromatography coupled with tandem mass spectroscopy (CEDRA Clinical Research).

THYROGLOBULIN ANALYSES AND TUMOR GENOTYPING

Blood samples were collected at baseline and at 4-week intervals, and serum thyroglobulin measurements were performed with the use of the Access 2 automated immunochemiluminometric assay (Beckman Coulter). Intraassay coefficients of variation were 3.3%, 1.7%, and 1.9% at 0.76, 7.0, and 106 ng per milliliter, respectively; interassay coefficients of variation over the 9-month period of measurement were 4.8%, 4.7%, and 5.0% at 0.75, 7.3, and 106 ng per milliliter, respectively.

Tumor DNA from 33 patients was centrally screened for mutations in *RET*, *B-type Raf kinase* (*BRAF*), *HRAS*, *KRAS*, *NRAS*, and *phosphatidylinositol-3-kinase, catalytic, alpha polypeptide* (*PIK3CA*), and for rearrangements of *RET-PTC1*, *RET-PTC3*, and *PAX8-peroxisome proliferator–activated receptor gamma 1* (*PPARγ1*). A detailed description of the methods is included in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

STATISTICAL ANALYSIS

We planned to enroll at least 80 patients to achieve a two-sided 95% confidence interval of 12 to 30% for the rate of an objective response, assuming an observed rate of 20%. All patients who received one dose or more of motesanib diphosphate were included in the efficacy and safety analyses. The overall tumor response was derived from multiple time-point responses as assessed by an independent radiographic review. The duration of the tumor response was the interval between the first, subsequently confirmed, objective response and evidence of progressive disease. The time to the response was the time from the first administration of the study drug to the initially documented (and subsequently confirmed) response. Progression-free survival was the time from the first administration of the drug to the date of radiographic evidence of disease progression or death. The duration of the response, progression-free survival, and overall survival were described with Kaplan–Meier estimates and 95% confidence intervals. The thyroglobulin analysis subgroup included all patients for whom baseline and one or more post-baseline measurements of thyroglobulin were available and who did not have detectable antithyroglobulin antibodies.

Amgen designed the study, in collaboration with the study cochairs, Drs. Sherman and Schlumberger. The academic authors had complete access to the study data and decided, with Amgen's support, to publish the study. Employees of Amgen collected and managed the data and performed the statistical analysis. An independent panel of radiologists from RadPharm, a commercial imaging laboratory, reviewed all radiographic assessments. Amgen and the study

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Table 1. Demographic and Baseline Characteristics of the Patients.

Characteristic	All Patients (N = 93)
Sex — no. (%)	
Female	44 (47)
Male	49 (53)
Age — yr	
Median	62
Range	36–81
Race or ethnic group — no. (%)*	
White	85 (91)
Asian	4 (4)
Hispanic or Latino	3 (3)
Black	1 (1)
Histologic subtype of differentiated thyroid cancer — no. (%)	
Papillary†	57 (61)
Hürthle cell	17 (18)
Follicular	15 (16)
Other‡	4 (4)
Time from initial diagnosis — yr§	
Median	4.4
Range	0.4–21.3
Extent of disease — no. (%)	
Locally advanced	1 (1)
Metastatic	92 (99)
No. of sites of disease — no. (%)	
1	26 (28)
2	39 (42)
≥3	28 (30)
ECOG performance status — no. (%)¶	
0	47 (51)
1	37 (40)
2	9 (10)
Prior therapy for thyroid cancer — no. (%)	
Thyroidectomy‖	93 (100)
Radioiodine therapy	
0 Courses	3 (3)
1 Course	14 (15)
2 Courses	35 (38)
≥3 Courses	41 (44)
External-beam radiation therapy	
0 Unique sites	40 (43)
1 Unique site	32 (34)
≥2 Unique sites	21 (23)

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Table 1. (Continued.)

Characteristic	All Patients (N = 93)
Chemotherapy	
0 Regimens	77 (83)
1 Regimen	10 (11)
≥2 Regimens	6 (6)
Time since most recent therapy for thyroid cancer — mo**	
Median	11.6
Range	1.2–367.2
Tumor genotyping — no. (%)††	
Mutation in *BRAF* (V600E)	10 (30)
Mutation in *HRAS* (Q61R)	1 (3)
Mutation in *KRAS* (G12C)	1 (3)
Mutation in *NRAS* (Q61R and Q61K)	4 (12)
Mutation in *RET*	0
Mutation in *PIK3CA*	0
RET-PTC1 rearrangement	0
RET-PTC3 rearrangement	0
PAX8-PPARγ1 rearrangement	0
No mutation or rearrangement identified	17 (52)

* Race or ethnic group was determined from patients' records.
† This category includes three patients with tumors that were classified histologically as a follicular variant of the papillary subtype.
‡ This category includes three patients with an insular variant of the follicular histologic subtype and one patient with a poorly differentiated histologic subtype.
§ Data were available for 80 patients.
¶ ECOG denotes Eastern Cooperative Oncology Group.
‖ Patients received subsequent thyrotropin-suppressive therapy or (less commonly) replacement therapy with levothyroxine.
** Data were available for 91 patients.
†† Data were available for 33 patients.

cochairs interpreted the data. The manuscript was written by the study cochairs, with assistance from Complete Healthcare Communications and Amgen and with contributions from all of the coauthors. The study cochairs attest to the completeness and accuracy of the data.

RESULTS

PATIENTS

Between July 29, 2005, and March 13, 2006, a total of 93 patients with differentiated thyroid cancer were enrolled in the study. All of the patients received one dose or more of motesanib diphosphate. A total of 32 patients completed 48 weeks of treatment. The remaining patients discontinued the drug because of disease progression (35 patients), adverse events (12), death (5), withdrawal of consent (1), an administrative decision (1), a protocol deviation (1), or the patient's request (6). The median length of treatment for all patients was 35 weeks (range, 0.4 to 56), and the median follow-up was 50 weeks (range, 1 to 77).

The most common histologic subtype was papillary thyroid carcinoma. At study entry, almost all of the patients had metastases, usually with multiple sites of disease, including lung (87%), lymph nodes (72%), and liver (26%). Disease progression according to RECIST within 6 months before study day 1 was documented in all patients by the investigator. Seventeen percent of the patients had previously received systemic chemotherapy (Table 1).

Table 1 summarizes the results of tumor geno-

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typing, which are shown in detail in Table 3 in the Supplementary Appendix. Of 25 patients with papillary thyroid carcinoma, 10 had tumors carrying the mutant *BRAF* V600E oncogene, and 4 had mutations in *RAS* genes (*HRAS* and *KRAS* in 1 patient each and *NRAS* in 2 patients).

EFFICACY

The primary end point of a confirmed objective response was achieved in 13 patients (14%; 95% confidence interval [CI], 7.7 to 22.7), all of whom had partial responses; the median time to the response was 15 weeks (95% CI, 8 to 27) (Table 2). Stable disease was observed in 62 patients (67%), with durable stable disease (i.e., disease that was stable for 24 weeks or more) in 33 patients (35%). Nine patients (10%) had unconfirmed partial responses that were classified as stable disease. Overall, 49% of the patients had either a confirmed partial response or durable stable disease. Disease progression was the best observed response in seven patients (8%). In 69 patients (74%), tumor measurements decreased from the baseline measurements (Fig. 1).

Of the 13 patients with an objective response, 4 had disease that subsequently progressed while the patients were taking the study medication. The Kaplan–Meier estimate of the median duration of a response was 32 weeks (the lower limit of the 95% CI was 24; the upper limit could not be estimated because of an insufficient number of events). The estimated median progression-free survival was 40 weeks (95% CI, 32 to 50) (Fig. 2A). The median overall survival was not estimable; the estimate of the survival rate at 12 months was 73% (95% CI, 63 to 83) (Fig. 2B).

There was no significant difference in the rate of the objective response between patients with the papillary or follicular variant of papillary carcinoma (57 patients) and those with the follicular or Hürthle-cell type (36 patients) (12% and 17%, respectively; P=0.56). We found no association between the presence or absence of the *BRAF* V600E mutation (10 and 15 patients, respectively) and the clinical outcome. Six of the 10 patients whose tumor contained the *BRAF* mutation had either a confirmed partial response or durable stable disease, as compared with 5 of the 15 patients without the mutation (Table 3 in the Supplementary Appendix).

SAFETY

A total of 87 patients (94%) had at least one treatment-related adverse event during the course of the study (Table 3). Twelve patients (13%) discontinued treatment owing to adverse events. The most commonly reported events were diarrhea, hypertension, fatigue, and weight loss; patients with hypertension were treated with antihypertensive medication, and those with diarrhea, fatigue, or weight loss received supportive care. Grade 3 events were reported in 51 patients (55%); 5 patients had a total of eight treatment-related grade 4 events (hypocalcemia in 2 patients and hyperuricemia, hypokalemia, cerebral hemorrhage, confusion, agitation, and oliguria in 1 patient each). There were two treatment-related deaths; both were due to pulmonary hemorrhage and occurred in patients in whom the disease had progressed. Several treatment-related events of interest (previously observed with anti-VEGF or anti-VEGF receptor therapies) were noted (Table 3). Increased thyrotropin concentrations, hypothyroidism, or both were reported in 22% of the patients. Five patients (5%) had cholecystitis (grade 2 in three patients and grade 3 in two patients). Two patients had treatment-related cardiac disorders; one had bradycardia, palpitations, and tachycardia, and one had myocardial ischemia (grade 2 in both patients).

PHARMACOKINETICS

Motesanib was rapidly absorbed, with a median time to the maximal plasma concentration (C_{max}) of 1.0 hour; the terminal half-life was approximately 6.7 hours. The mean (±SD) motesanib C_{max} value (787±526 ng per milliliter [2.10±1.41 μmol per liter]) and area under the plasma concentration–time curve ($AUC_{0\text{-}24}$, 3.99±1.42 μg × hour per milliliter [10.7±3.79 μmol × hour per liter]) were similar to those observed for the 125-mg dose in another study of motesanib as monotherapy for solid tumors.[13] Between weeks 4 and 24, the median trough plasma concentration (C_{min}), measured in 9 to 23 patients at different time points, ranged from 8.50 to 26.3 ng per milliliter (22.7 to 70.3 nmol per liter) and was consistently above the IC_{50} value (4 ng per milliliter [10 nmol per liter]) for inhibition of the proliferation of human umbilical-vein endothelial cells in vitro.[12]

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Table 2. Tumor Response According to RECIST and Independent Review.*

Variable	All Patients (N=93)
Assessment of response — no. (%)	
Complete response	0
Partial response	13 (14)
Stable disease	62 (67)
Unconfirmed partial response classified as stable disease†	9 (10)
Durable stable disease (≥24 wk)	33 (35)
Progressive disease	7 (8)
No data on response available‡	11 (12)
Objective response — % (95% CI)	14 (7.7–22.7)
Clinical benefit — no. (%)§	46 (49)
Time to tumor response — wk	
Median	15
95% CI	8–27
Duration of partial response	
Censored data — no./total no. (%)¶	8/13 (62)
Patients who had a relapse — no./total no. (%)	5/13 (38)
Kaplan–Meier estimate of median duration — wk (95% CI)	32 (24–NE)
Progression-free survival	
Alive with no progression — no. (%)	43 (46)
Progression or death — no. (%)	50 (54)
Kaplan–Meier estimate of median progression-free survival — wk (95% CI)	40 (32–50)
Kaplan–Meier estimate of progression-free survival rate — % (95% CI)	
Week 16	78 (69–87)
Week 32	60 (50–71)
Week 48	37 (24–50)
Overall survival	
Patients who survived — no. (%)	66 (71)
Patients who died — no. (%)	27 (29)
Kaplan–Meier estimate of median overall survival — mo (95% CI)	NE
Kaplan–Meier estimate of survival rate — % (95% CI)	
Month 4	89 (82–95)
Month 8	82 (74–90)
Month 12	73 (63–83)

* NE denotes not estimable (insufficient number of events).
† Seven patients had a single assessment of partial response with a subsequent assessment of progressive disease or had no additional tumor assessment; two patients with follicular or Hürthle-cell carcinoma did not have the required bone scans to confirm partial response.
‡ No week 8 scans were available (scans were obtained before day 47 or no radiographic assessments were performed), available scans were not interpretable, or no baseline scans were available.
§ Clinical benefit was defined as either a confirmed partial response or durable stable disease.
¶ Data for patients with a confirmed objective response and no assessment of disease progression during the study are included as censored data at the time of the last disease assessment.

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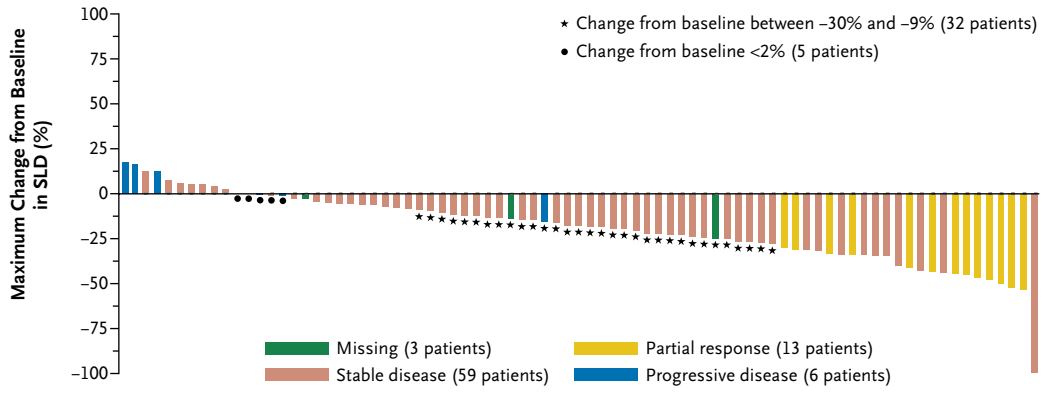

Figure 1. Maximum Percent Change from Baseline in the Sum of the Longest Diameters (SLD) of Target Lesions.
The change from baseline in tumor measurement as assessed by an independent review is shown for 81 patients. Not shown are data for three patients with stable disease (only nontarget lesions at baseline according to an independent review), one patient with progressive disease due to a new lesion (SLD unavailable), and eight patients with no radiographic assessments available (no information on disease response and no SLD measurements). In three of the patients with missing information on tumor response, SLD measurements were performed before week 8. An unconfirmed partial response was classified as stable disease in nine patients. One additional patient had more than a 30% decrease from baseline in SLD but had progression in a nontarget lesion. Target and nontarget lesions are defined according to the Response Evaluation Criteria in Solid Tumors (RECIST).[14]

THYROGLOBULIN ANALYSES

Of the 75 patients in whom thyroglobulin analysis was performed, 61 (81%) had serum thyroglobulin concentrations that decreased from baseline during the study. In 34 patients (45%) the decrease was 50% or more, and that decrease was sustained for 24 weeks or more in 11 patients (15%). A correlation was observed between a decrease from baseline of 50% or more in thyroglobulin concentration and a decrease from baseline of 30% or more in the sum of the longest diameter of target tumor lesions (Spearman's rank correlation coefficient, 0.472; P<0.001).

DISCUSSION

The treatment for progressive, advanced or metastatic differentiated thyroid cancer has been limited to surgery, radioiodine therapy, external-beam radiation therapy, or a combination of these treatments. In patients with radioiodine-resistant disease, cytotoxic chemotherapy yields low response rates of short duration, is often associated with considerable toxicity, and does not prolong survival.[15-17] Recently, angiogenesis has been explored as a target for the treatment of advanced thyroid cancer. A study of thalidomide, which has several actions, including the inhibition of angiogenesis, showed that 5 of 28 patients with a variety of thyroid cancers had unconfirmed partial responses on the basis of criteria other than RECIST.[18]

We found that 13 of 93 patients with progressive, radioiodine-resistant, locally advanced or metastatic differentiated thyroid cancer who received 125 mg of motesanib diphosphate once daily had a partial response. Of these 93 patients, 87 had at least one adverse event, and 51 had a grade 3 adverse event. The response to motesanib diphosphate, which inhibits multiple signaling pathways that are involved in differentiated thyroid tumorigenesis, including VEGF and platelet-derived growth-factor receptors,[12] suggests that inhibiting angiogenesis in differentiated thyroid cancer may be clinically useful. Recent preliminary data suggest that other inhibitors of VEGF receptors have efficacy in advanced thyroid cancer.[19,20] In a single-institution trial of sorafenib, the confirmed partial response rate among 58 patients with metastatic papillary thyroid carcinoma was 3%.[20] In our study of 93 patients with progressive differentiated thyroid cancer, the proportion of patients who had stable disease (67%), the proportion who had durable stable disease (35%) and the median progression-free survival (40 weeks [95% CI, 32 to 50]) all suggest clinically meaningful tumor control. In contrast, no partial or complete responses were seen in a

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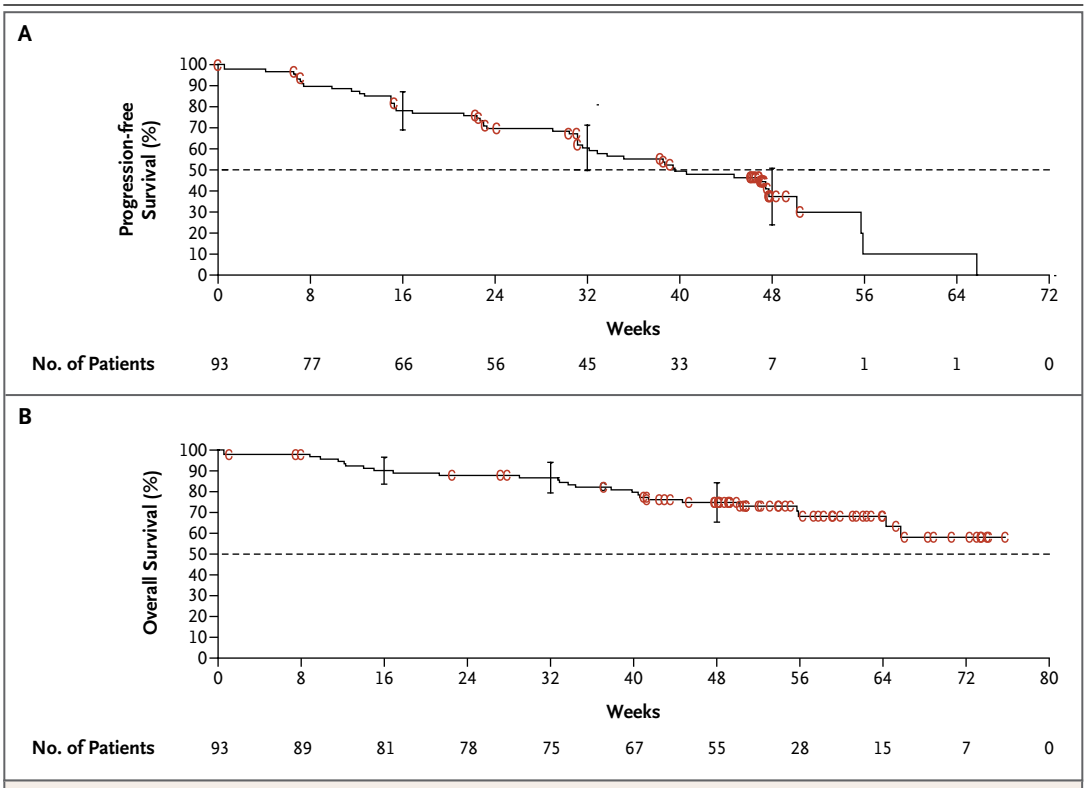

Figure 2. Kaplan–Meier Analysis of Progression-free Survival and Overall Survival.

Panel A shows progression-free survival among all 93 patients who received at least one dose of motesanib diphosphate. Panel B shows overall survival among the same patients. Eight patients died during the course of the study, within 30 days after the last administration of motesanib diphosphate; 19 additional patients died during long-term follow-up. The I bars indicate 95% confidence intervals. C denotes censored observation.

phase 2 study of gefitinib, an inhibitor of the epidermal growth factor receptor, among 18 patients with advanced differentiated thyroid cancer, and the progression-free survival time was only 3.7 months (95% CI, 1.8 to 5.7).[21]

Changes in the thyroglobulin concentration are used to monitor residual tumor volume, recurrent or metastatic tumor growth, or both in patients with differentiated thyroid cancer.[22,23] The decrease in serum thyroglobulin levels that we found in most patients and its correlation with the tumor response are consistent with the findings previously reported for radioiodine therapy.[24] The magnitude of this effect was probably underestimated because thyrotropin promotes thyroglobulin secretion, and treatment with motesanib diphosphate caused increased serum concentrations of thyrotropin.

We attempted to correlate the tumor genotype and clinical response in differentiated thyroid cancer, but the number of tumors available to be studied was too small to draw conclusions about an association of responsiveness with *BRAF* mutations that influence the VEGF-signaling pathway.[25]

Two adverse events related to motesanib diphosphate treatment are worth mentioning. Hypothyroidism, an increase in the thyrotropin concentration, or both occurred in 22% of the patients and have recently been reported during treatment with the multikinase inhibitors sunitinib,[26] imatinib,[27] and possibly sorafenib.[28] In athyreotic patients (patients whose thyroids were surgically resected), motesanib diphosphate may induce alterations in the absorption or metabolism of thyroxine instead of affecting thyroid hormone synthesis, a mechanism that is implicated in sunitinib-induced hypothyroidism.[26] Given these multiple effects on thyroid function, we suggest close monitoring of thyrotropin levels and adjustments in the dose of levothyroxine, as appropriate, in patients who are receiving multikinase inhibitors. In five patients in our study (5%), chole-

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Table 3. Treatment-Related Adverse Events and Related Adverse Events of Interest in the 93 Patients.

Event	All Grades	Grade 3	Grade 4	Grade 5
		no. of patients (%)		
All treatment-related adverse events				
Adverse events	87 (94)	51 (55)	5 (5)	2 (2)
Serious adverse events	19 (20)	8 (9)	5 (5)	2 (2)
Treatment-related adverse events in ≥10% of patients				
Diarrhea	55 (59)	12 (13)	0	0
Hypertension	52 (56)	23 (25)	0	0
Fatigue	43 (46)	4 (4)	0	0
Weight loss	37 (40)	5 (5)	0	0
Abdominal pain	28 (30)	5 (5)	0	0
Nausea	26 (28)	2 (2)	0	0
Anorexia	25 (27)	4 (4)	0	0
Headache	24 (26)	3 (3)	0	0
Dry mouth	13 (14)	0	0	0
Hypothyroidism	11 (12)	0	0	0
Vomiting	11 (12)	1 (1)	0	0
Increased thyrotropin	11 (12)	0	0	0
Asthenia	10 (11)	0	0	0
Arthralgia	9 (10)	1 (1)	0	0
Related adverse events of interest*				
Hypothyroidism, increased thyrotropin, or both	20 (22)	0	0	0
Hemorrhage	13 (14)	1 (1)	1 (1)	2 (2)
Gallbladder toxicity†	12 (13)	2 (2)	0	0
Thromboembolic events	2 (2)	1 (1)	0	0
Cardiac disorders‡	2 (2)	0	0	0

* Adverse events of interest are those previously observed with anti-VEGF or anti-VEGF receptor therapies.
† Gallbladder toxicity included biliary cholic, cholecystitis, acute cholecystitis, cholelithiasis, gallbladder enlargement, and gallbladder edema.
‡ Cardiac disorders included bradycardia, palpitations, and tachycardia (in one patient) and myocardial ischemia (in one).

cystitis developed, a complication that has not previously been reported in association with antiangiogenic therapy. These five patients presented with classic symptoms (right-upper-quadrant pain and fever) and had a response to medical or surgical treatment (or both), including cholecystectomy. This incidence of cholecystitis is higher than expected on the basis of other studies of motesanib diphosphate; however, the cause is unknown and the relation to motesanib diphosphate is under investigation.

The key limitation of this trial was the lack of randomization with a control group. Because the study group specifically included patients with advanced differentiated thyroid cancer, traditional comparator therapies, such as cytotoxic chemotherapy, were inappropriate owing to their ineffectiveness and toxicity. However, we believe that the large number of patients enrolled in this study allowed a reasonable estimate of clinical benefit.

In conclusion, motesanib diphosphate may be an effective treatment in some patients with progressive, metastatic, radioiodine-resistant differentiated thyroid cancer. However, a broader applicability of treatment that inhibits angiogenesis

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in thyroid cancer needs to be established in further studies.

ADDENDUM

Therapy with the multikinase inhibitor sorafenib has been reported to yield a 26% partial response rate in patients with metastatic differentiated thyroid carcinoma.[29]

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APPENDIX

In addition to the authors, the following investigators participated in the study: *University Hospital for Nuclear Medicine and Endocrinology, Klagenfurt, Austria* — P. Lind; *University Hospital for Nuclear Medicine and Endocrinology, Salzburg, Austria* — C. Pirich; *University Hospital St. Luc, Brussels* — C. Daumerie; *Institut Gustave Roussy, Villejuif, France* — E. Baudin; *Institut Bergonié, Bordeaux, France* — B.N. Bui; *Centre Hospitalier Universitaire (CHU) de la Timone, Marseille, France* — B. Conte-Devolx; *CHU Angers, Angers, France* — V. Rohmer; *Institut Jean Godinot, Reims, France* — C. Schvartz; *Belgyogyaszati Hospital, Budapest, Hungary* — I. Szabolcs, K. Racz; *University Hospital, Florence, Italy* — M.L. Brandi; *University Hospital, Pisa, Italy* — A. Pinchera, R. Elisei; *Hospital S. Luigi Gonzaga, Orbassano, Italy* — F. Orlandi; *University Hospital, Siena, Italy* — F. Pacini; *Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland* — B. Jarzab; *Oddzial Clinic of Endocrinology, Poznan, Poland* — J. Sowinski; *Sahlgrenska University Hospital, Göteborg, Sweden* — S. Jansson; *Karolinska University Hospital, Stockholm* — G. Lundell, A. Hallqvist; *University Hospital, Geneva* — C. Meier, J. Philippe; *University of Pittsburgh Cancer Institute, Pittsburgh* — S. Agarwala; *Henry Ford Health System, Detroit* — H. Ali; *Mission International Medical Group, Mission Viejo, CA* — J. Barrera; *Center for Cancer and Blood Disorders, Bethesda, MD* — R. Boccia; *Cleveland Clinic Foundation, Cleveland* — R. Bukowski; *Washington Hospital Center, Washington, DC* — K. Burman; *University of California, San Francisco, San Francisco* — O. Clark; *Dartmouth–Hitchcock Medical Center, Lebanon, NH* — T. Davis; *University of Texas M.D. Anderson Cancer Center, Houston* — A. Hoff, N. Sarlis; *Lakeland Regional Cancer Center, Lakeland, FL* — J. Jakub; *Providence St. Joseph Medical Center, Burbank, CA* — R. Mena; *University of Cincinnati Barrett Cancer Center, Cincinnati* — Z. Nahleh; *Premiere Oncology Medical Corporation, Santa Monica, CA* — L. Rosen; *Cancer Center of the Carolinas, Greenville, SC* — J. Stephenson; *Sparrow Regional Cancer Center, Lansing, MI* — G. Srkalovic; *Pacific Shores Medical Group, Long Beach, CA* — N. Tchekmedyian.

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