Phase II Study of Daily Sunitinib in FDG-PET–Positive, Iodine-Refractory Differentiated Thyroid Cancer and Metastatic Medullary Carcinoma of the Thyroid with Functional Imaging Correlation

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Abstract

Purpose: We conducted a phase II study to assess the efficacy of continuous dosing of sunitinib in patients with flurodeoxyglucose positron emission tomography (FDG-PET)–avid, iodine-refractory well-differentiated thyroid carcinoma (WDTC) and medullary thyroid cancer (MTC) and to assess for early response per FDG-PET.

Experimental Design: Patients had metastatic, iodine-refractory WDTC or MTC with FDG-PET–avid disease. Sunitinib was administered at 37.5 mg daily on a continuous basis. The primary end point was response rate per Response Evaluation Criteria in Solid Tumors (RECIST). Secondary end points included toxicity, overall survival, and time to progression. We conducted an exploratory analysis of FDG-PET response after 7 days of treatment.

Results: Thirty-five patients were enrolled (7 MTC, 28 WDTC), and 33 patients were evaluable for disease response. The primary end point, objective response rate per RECIST, was 11 patients (31%; 95% confidence interval, 16-47%). There were 1 complete response (3%), 10 partial responses (28%), and 16 patients (46%) with stable disease. Progressive disease was seen in 6 patients (17%). The median time to progression was 12.8 months (95% confidence interval, 8.9 months-not reached). Repeat FDG-PET was done on 22 patients. The median percent change in average standardized uptake values was −11.7%, −13.9%, and 8.6% for patients with RECIST response, stable disease, and progressive disease, respectively. Differences between response categories were statistically significant (P = 0.03). The most common toxicities seen included fatigue (11%), neutropenia (34%), hand/foot syndrome (17%), diarrhea (17%), and leukopenia (31%). One patient on anticoagulation died of gastrointestinal bleeding.

Conclusion: Continuous administration of sunitinib was effective in patients with iodine-refractory WDTC and MTC. Further study is warranted.

Thyroid carcinoma is a common malignancy with more than 30,000 cases predicted in the United States in 2008 (1). The survival of patients with metastatic medullary carcinoma of the thyroid (MTC) or radioiodine-refractory well-differentiated thyroid carcinoma (WDTC) is variable (2, 3). Whereas some patients may have indolent disease, even when widely metastatic, others may experience rapid disease progression. Recent work has shown that patients with iodine-refractory WDTC that is hypermetabolic on flurodeoxyglucose positron emission topography (FDG-PET) are more likely to have progressive disease and have a median survival of less than 5 years (4). Thus, in iodine-refractory cancer, FDG-PET is increasingly used to select patients in whom systemic therapy should be considered (5). In this regard, the requirement for uptake on FDG-PET may select for more aggressive disease and provides a basis for more uniform patient selection compared with more traditional selection criteria such as evidence of disease progression by changes in tumor size. In addition, by detecting metabolic changes within the tumor, FDG-PET may be able to provide an early assessment of treatment effect.

Sunitinib is a multitargeted tyrosine kinase inhibitor (TKI). Targets of the drug include vascular endothelial...
growth factor receptor (VEGFR) types 1 and 2, platelet-derived growth factor receptors, c-KIT, FLT3, and RET (6). The inhibitory effect of the drug on VEGF and RET makes it a rational candidate for the therapy of WDTC and MTC. Somatic mutations of the proto-oncogene RET are important in the development of MTC. Point mutations and rearrangements of RET are also present in 2% to 60% of patients with papillary carcinoma of the thyroid (7, 8). In addition, elevated serum levels of vascular endothelial growth factor are also associated with poor prognosis in papillary carcinoma of the thyroid (9). Sunitinib is currently approved for the therapy of renal cell carcinoma and gastrointestinal stromal tumor (GIST) on an intermittent treatment schedule (10). Recent data suggest that the continuous administration of 37.5 mg/d may be a reasonable alternative to the intermittent dosing of the drug (11).

We hypothesized that sunitinib would be effective in treating MTC and iodine-refractory WDTC. We conducted a single-institution, phase II trial of continuous administration sunitinib in patients with metastatic, iodine-refractory WDTC or metastatic MTC. The primary goal of our study was objective response to sunitinib by sized-based criteria [Response Evaluation Criteria in Solid Tumors (RECIST)]. Evidence of metastatic, iodine-refractory WDTC or metastatic MTC was required for participation. A positive FDG-PET scan was also an entry criterion for the study. In addition, we performed a FDG-PET scan after 1 week of sunitinib therapy as an exploratory study to assess early response based on data from FDG-PET in GISTs treated with sunitinib.

Materials and Methods

Patients

Patients were eligible for the study if they were at least 18 years old and had metastatic WDTC or MTC, evidence of refractoriness to iodine therapy for WDTC (documented by a combination of nuclear imaging and thyroglobulin levels), an Eastern Cooperative Oncology Group performance status of 0 to 3, evidence of FDG-PET uptake by tumor lesions, measurable disease defined by RECIST, resolution of all acute toxic effects from prior therapy to grade ≤1 [National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 3.0], total serum bilirubin ≤1.5 × upper limit of normal (ULN), serum transaminases <2.5 × ULN or <5.0 × ULN if secondary to liver metastases, serum creatinine ≤1.5 × ULN, absolute neutrophil count (ANC) ≥1.5 × 10⁹/L, platelet count ≥100,000/μL, and hemoglobin ≥9.0 g/dL. FDG-PET or PET/computed tomography (CT) used in the entry criteria was reviewed by an experienced nuclear medicine physician to confirm positivity before patient entry (see PET/CT interpretive criteria below). All patients signed a written informed consent form before enrollment. The institution's Internal Review Board approved the study protocol.

Patients were ineligible for the study if they had symptoms, untreated brain metastasis; a second primary malignancy; type I diabetes mellitus; type II diabetes mellitus with fasting glucose levels greater than 150 mg/dL; uncontrolled hypertension; or major surgery or radiation therapy within 4 weeks of starting the study treatment. Pregnant or breast-feeding women and patients who had any of the following events within the 6 months before study enrollment were excluded: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, or ongoing cardiac arrhythmias of grade ≥2. The protocol was amended to exclude patients receiving full-dose anticoagulation or with history of hemoptysis (of at least 2.5 mL per episode) within 3 months unless definitively treated with surgery or radiation.

Study treatment

Patients received sunitinib orally at an initial dose of 37.5 mg to be taken daily until disease progression, unacceptable toxicity, or consent withdrawal. Patients with grade ≥3 toxicities discontinued sunitinib until recovery to grade ≤2. Sunitinib was held for ANC <0.75 × 10⁹ cells/L. After holding sunitinib, patients restarted sunitinib at the initial dose or reduced to 25 mg daily. Patients who had a dose reduction could not reescalate the dose to 37.5 mg. Patients who had sunitinib held for longer than 14 days were withdrawn from the study.

Evaluation and follow-up

Screening evaluation consisted of history and physical examination, CT scans of involved sites, serum chemistries, pregnancy test, complete blood counts, thyroid-stimulating hormone, free T4, and tumor markers (thyroglobulin for WDTC, calcitonin for MTC). Follow-up evaluations consisted of monthly history and physical examination, assessment of adverse events, complete blood counts, and chemistries. Imaging and tumor marker follow-up studies...
consisted of CT scans every 3 months or sooner if clinically indicated. CT scans used for response evaluation were fully diagnostic CT scans that included all sites of metastases. These studies were done separately from low-dose noncontrast CT used for attenuation correction and anatomic localization for PET/CT. Contrast enhancement was used for most of the diagnostic CT scans, especially for patients with regional nodal or liver metastases, for which contrast is important for tumor delineation. Response was categorized by the change in lesion diameter based on CT, using standard RECIST (12). PET scans were repeated at 1 week after the initial dose, at the option of the patient and referring physician, as an exploratory early indicator of response. Patients were followed until tumor progression, death, or study discontinuation for unacceptable toxicity or consent withdrawal, up to 2 years from the date of the last dose of sunitinib.

**PET imaging and analysis**

FDG-PET and PET/CT patient preparation and image acquisition were done according to the National Cancer Institute consensus guidelines (13). Patients fasted at least 6 hours before imaging and had plasma glucose assayed before FDG injection to rule out significant hyperglycemia. All imaging was done on either an ADVANCE PET tomograph or a Discovery STE PET/CT tomograph (GE Medical Systems). The majority of baseline studies were done using PET/CT. Follow-up studies were done on the same device as baseline where possible; however, even in the cases where a different device was used, tomographs were regularly cross-calibrated to ensure reproducible standardized uptake values (SUV). Imaging was done over 5 to 6 adjacent imaging fields covering the skull to mid-thighs starting 60 ± 10 minutes after injection. Images included 7-minute emission scans per axial field-of-view. For PET/CT, low-dose noncontrast CT was used for attenuation correction and anatomic localization. For PET-only scans, 3-minute transmission scans per axial field-of-view with image segmentation were used for attenuation correction. All baseline images underwent initial review by nuclear medicine physicians experienced in PET as part of standard clinical care. For entry into the study, all baseline images were reviewed by a single reviewer with significant experience in PET interpretation. Clear-cut evidence of uptake greater than blood pool in a location consistent with thyroid cancer metastasis and correlating to findings on diagnostic CT or PET/CT were considered evidence of FDG-positive thyroid cancer for entry into the study.

For the exploratory study of FDG-PET as a predictor of response to sunitinib, the maximum lesion SUV and the average SUV of up to 9 lesions served as a quantitative measure of FDG uptake. We recorded baseline and 1-week maximum SUVs for up to the 9 most avid individual lesions per patient and categorized the lesions as nodal, lung, bone, liver, or neck mass metastasis. Because there are no accepted criteria for response, the percent change in FDG uptake from the baseline to 1-week scan was recorded using both the single lesion with the highest SUV on the baseline scans and the average of maximum SUV of up to 9 recorded lesions. Images were also reviewed qualitatively to ensure that subjective impressions matched quantitative results.

**Study end points**

The primary end point was the overall response rate based on RECIST at the time of maximal response (12). Secondary end points included evaluation of time to tumor progression (TTP), overall survival (OS), and the safety and toxicity profiles of continuous daily treatment with sunitinib in this population. Tumor marker change from baseline was also recorded. A tumor marker response was defined empirically as a 50% decrease from the baseline, given the absence of an established cutoff for response (14). Patients with elevated thyroglobulin antibodies were not considered evaluable for thyroglobulin tumor marker response (15). We conducted exploratory analyses of early FDG-PET and tumor marker responses and their association with radiographic response and TTP.

**Statistical analysis**

We calculated a sample size of 35 patients with the assumption that 30 patients would undergo evaluation for tumor response. This confers a power of 92% if the null hypothesis is a response rate ≤10% and the alternative hypothesis is a response rate ≥33% at a two-sided α level of 0.05. We postulated that a true response rate <10% was not likely to be clinically important. We reported adverse events as proportions for each adverse event of NCI-CTCAE grade 3 or higher. We reported response rate as the proportion and 95% confidence interval (95% CI) of patients who achieved a complete response or partial response. We reported duration of response, TTP, and OS as median values with their respective 95% CIs.

**FDG-PET scan exploratory analysis.** For the exploratory analysis of serial FDG-PET SUV changes, we used one-way ANOVA to test the association of RECIST response (categorized as response, stable, or tumor progression) with percent SUV changes for both the most PET-avid lesion and the average maximum of up to 9 lesions at 1 week. We estimated the pairwise Pearson correlation coefficient between average percent SUV changes and changes in tumor size measured at the time of RECIST assessment. For the analysis of FDG-PET changes by type of metastatic lesion, we used a χ² test for the association of dichotomized FDG-PET response with the type of lesion (nodal, lung, bone, liver, or neck mass). Based on published estimates of SUV precision, a decline of 20% or more in the average maximum SUV was considered a PET response for the purpose of this analysis (16). We used a one-way ANOVA to test the association of average SUV percent changes with type of metastatic lesion. We applied the Cox proportional hazards regression model to test the association of PET changes (average percent SUV changes from baseline as a continuous variable) and time-to-tumor progression.
Tumor marker exploratory analysis. We calculated the positive predictive value and negative predictive value for thyroglobulin response and response by RECIST in patients with WDTC. We used a Fisher’s exact test for the association of response by thyroglobulin and by RECIST. We did not test the validity of calcitonin response in MTC because there were only 6 patients with MTC.

We considered results as statistically significant for $P$ values <0.05. All statistical tests were two-sided. We performed all statistical analyzes with STATA SE11 software.

Results

Baseline characteristics

Between August 2007 and February 2009, 35 patients with recurrent or metastatic WDTC or MTC were enrolled in the study. All patients had disease with increased metabolic activity per FDG-PET, and all patients with WDTC were radioiodine refractory. A total of 33 patients were available for evaluation of response; 1 patient did not have measurable disease per RECIST at baseline, and 1 patient was removed from study due to an adverse event before evaluation. Twenty-four patients underwent repeat evaluation with FDG-PET after 7 days of therapy. The lesions with the highest SUV per FDG-PET were most often located in the lung and lymph nodes. Patient demographics are listed in Table 1. The study population was primarily composed of WDTC subtypes (80%; predominately papillary thyroid carcinoma). The patients had good performance status and were heavily pretreated with radioiodine therapy. Four patients had been previously treated with a TKI.

Efficacy

A total of 35 patients were treated with sunitinib and all were included in the intent-to-treat analysis. Two patients were not evaluable for response for the reasons mentioned earlier. The median duration of treatment for all patients was 8.5 months, with 11 patients remaining on trial. The median follow-up was 15.5 months (range, 1-25.5 months). The primary end point, objective response rate per RECIST, was documented in 11 patients (response rate, 31%; 95% CI, 16-47%; Table 2). Eight of 29 patients with WDTC and 3 of 6 patients with MTC achieved a RECIST response (response rate, 28% and 50% for WDTC and MTC, respectively). There were 1 complete response (3%) and 10 partial responses (28%). In addition, 16 patients (46%) had stable disease. Thus, 77% (95% CI, 63-91%) did not have disease progression at the first evaluation at 3 months, whereas progressive disease was seen in 17% (95% CI, 7-35%). The maximum percent change in tumor size from baseline for each patient is illustrated in Fig. 1A. One patient was not considered evaluable for response due to lack of measurable disease at baseline. At treatment initiation, this patient had multiple, subcentimeter pulmonary nodules associated with symptomatic dyspnea requiring 2 liters of supplemental oxygen per nasal canula. Although early review of his CT scans suggested evaluable disease, subsequent rereview found no lesions of sufficient size to meet the RECIST. After 3 months on study drug, he was off supplemental oxygen and showed a significant decrease in the size and number of pulmonary nodules.

The current study included four patients previously treated with oral TKIs. Two were enrolled in a clinical trial with motesanib and two were treated with sorafenib. The two patients treated with motesanib had stable disease on the drug and were on therapy for more than 1 year. One of these patients had a partial response to sunitinib and the other had progressive disease at initial evaluation. The two patients previously treated with sorafenib had the drug discontinued secondary to toxicity. One of these patients had a 29% reduction of tumor by RECIST (stable disease) in the current study and was on therapy for 12 months.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (51)</td>
</tr>
<tr>
<td>Male</td>
<td>17 (49)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>61</td>
</tr>
<tr>
<td>Range</td>
<td>34-73</td>
</tr>
<tr>
<td>Race/ethnic group</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>29 (76)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>18 (51)</td>
</tr>
<tr>
<td>Follicular</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Hurthle cell</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Insular</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Medullary</td>
<td>7 (20)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0/1</td>
<td>33 (94)</td>
</tr>
<tr>
<td>2/3</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Prior therapy</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>34 (97)</td>
</tr>
<tr>
<td>Iodine-131 treatment</td>
<td>27 (77)</td>
</tr>
<tr>
<td>External beam radiation</td>
<td>21 (60)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>6 (17)</td>
</tr>
<tr>
<td>TKI (2 sorafenib, 2 motesanib)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Location of primary FDG-PET–avid lesion</td>
<td></td>
</tr>
<tr>
<td>Lymph node</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Liver</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Bone</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Lung</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Neck</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
FDG-PET response and exploratory analysis

**FDG-PET and RECIST response.** Twenty-four patients underwent evaluation by FDG-PET both at baseline and after 7 days of sunitinib therapy. Of these patients, 22 were evaluable by RECIST. The remaining patients either chose not to undergo repeat FDG-PET (exploratory and optional for this study) or had undergone outside FDG-PET studies at baseline, which were useful for determining evidence of tumor FDG uptake for study entry criteria but not for quantitative comparison to follow-up PET carried out at our center. The median number of PET lesions per patient was 4 (SD, 1.87; range, 1-9).

At baseline, the median average SUV and SUV for the most PET-avid lesions were 7.9 (SD, 16.2; range, 3.3-59.6), and 13.0 (SD, 20.5; range, 3.8-67.0), respectively, indicating highly metabolically active lesions. The median percent change from baseline in average SUVs was −11.7% (SD, 29.5%;  

Of the 11 patients with an objective disease response, 6 have subsequently had progressive disease per RECIST. The median duration of response was 8.0 months (95% CI, 3.2-15.6 months). The median OS has not been reached; nine patients have died during the follow up period. The median TTP per Kaplan-Meier analysis was 12.8 months (95% CI, 8.9 months-not reached; Fig. 1B).

### Table 2. Response to treatment

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients (N = 35)</th>
<th>%</th>
<th>Median percent change in average SUV (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1</td>
<td>3</td>
<td>−78.8, n = 1</td>
</tr>
<tr>
<td>Partial response</td>
<td>10</td>
<td>28</td>
<td>−10.0 (−0.5 to −22.9), n = 5</td>
</tr>
<tr>
<td>Stable disease total</td>
<td>16</td>
<td>46</td>
<td>−13.9 (34.4 to 11.5), n = 12</td>
</tr>
<tr>
<td>Stable disease &gt;6 mo</td>
<td>13</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6</td>
<td>17</td>
<td>8.6 (−0.8 to 36.1), n = 4</td>
</tr>
<tr>
<td>Not assessable</td>
<td>2</td>
<td>6</td>
<td>n = 13</td>
</tr>
<tr>
<td>Objective response rate (95% CI)</td>
<td>11</td>
<td>31 (16-47)</td>
<td></td>
</tr>
<tr>
<td>Disease control rate (95% CI)</td>
<td>27</td>
<td>77 (63-91)</td>
<td></td>
</tr>
<tr>
<td>Disease control by histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WDTC</td>
<td>22/28</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>MTC</td>
<td>5/7</td>
<td>71</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Disease control rate includes patients with complete response, partial response, and stable disease at 3 mo.

The cent change from baseline in average SUVs was −3.9% (SD, 15.2%;  

### Exploratory analysis of FDG-PET by type of lesion.

The total number of PET metastatic lesions was 86. Twenty-eight (33%) lesions were in the lymph nodes, 26 (30%) in the lungs, 15 (17%) in the bones, 11 (13%) in the neck or thyroid bed, and 6 (7%) in the liver. Twenty-eight (33%) lesions showed a PET response (>20% SUV decline). The number of PET responses of >20% by type of lesion was 9 (32%) for lymph nodes, 12 (46%) for lung, 5 (33%) for bone, 2 (18%) for neck or thyroid bed, and zero (0%) for liver metastasis. There were no statistically significant associations between the type of metastatic lesion and dichotomized PET response (>20% decline in SUV) or changes in average SUV from baseline (P = 0.19 and P = 0.91, respectively). The lack of association between the type of metastatic lesion and the PET response suggests that analysis of a single index lesion may be feasible.
Tumor marker analysis

A total of 19 patients had baseline and serial thyroglobulin levels drawn while on sunitinib. Of these, 58% (11 patients) had a decrease in serum thyroglobulin levels of 50% or greater (mean decrease of 56%). Of the patients with WDTC, a 50% change in thyroglobulin levels had a positive predictive value for RECIST response of 54% and a negative predictive value of 75%. There was no significant association between a 50% change in serum tumor marker and response per RECIST ($P = 0.35$). Six patients with MTC had baseline and serial calcitonin levels drawn during treatment. Although there are too few patients to determine statistical significance, all three patients who had a 50% decrease in calcitonin levels while on sunitinib had disease control (lack of progression).

Safety

Patients were treated with continuous dosing of sunitinib at 37.5 mg/d. Dose reduction to 25 mg/d was required in 21 of 35 treated patients (60%). There was no association between previous therapy, including use of TKIs, and the need for dose reduction. Sixteen patients (45%) had their dose reduced after the protocol was modified to allow for drug continuation with an ANC $>0.75 \times 10^9$ cell/L. These patients had been on therapy for a median of 3.5 months. There were no incidents of neutropenic fever. All patients who had a dose reduction remained at 25 mg per protocol requirements. Four patients discontinued treatment due to toxicity; two patients developed grade 2 hemoptysis, one patient developed grade 3 diarrhea, and one patient died on study due to gastrointestinal bleeding.

Fig. 1. A, maximum percent change in target lesions from baseline in all patients with evaluable disease ($n = 33$; 1 patient was removed from the study because of adverse event before evaluation and 1 patient did not have measurable disease per RECIST at baseline). Blue bars, WDTC; green bars, MTC. B, Kaplan-Meier estimate of TTP. The median TTP per Kaplan-Meier analysis is 12.8 mo (95% CI, 8.9 mo-not reached). C, Kaplan-Meier estimate of OS. The median OS has not been reached; 9 patients have died during the follow-up period.
(this patient was on full-dose anticoagulation with low molecular weight heparin for a previous pulmonary embolism). Two other patients required admission for bleeding episodes. One was on warfarin for atrial fibrillation. After these events, the exclusion criteria were modified to exclude patients on full-dose anticoagulation. The reasons for dose reduction include the following grade 3 toxicities: fatigue (11%), dehydration (3%), mucositis (3%), diarrhea (17%), gastrointestinal bleeding (6%), hand/foot syndrome (17%), cytopenias (46%), hypocalcemia (3%), peripheral neuropathy (3%), supraventricular tachycardia (6%), laryngeal edema (3%), odynophagia (3%), and infection without neutropenia (3%). The most common adverse events were fatigue, diarrhea, hand/foot syndrome, and neutropenia (Table 3). These events have been reported in previous studies with sunitinib (11).

**Discussion**

The response rates to conventional chemotherapy are low in patients with WDTC requiring palliation of symptoms (2, 3). In addition, many patients have asymptomatic progressive disease, and it is important that palliative treatments do not worsen a patient's quality of life. Recently, multitargeted TKIs have shown significant activity in patients with iodine-refractory WDTC and MTC (15, 17–20). The activity of these agents has been consistently superior to conventional chemotherapy and associated with a favorable side effect profile. Table 4 summarizes the efficacy results from these trials. The studies have shown long intervals of progression-free survival, which suggest a change in the natural history of the disease. Because many patients with these tumors can have an indolent course that does not require therapy, most trials have attempted to select patients with more aggressive disease. Some trials have required documentation of disease progression by RECIST over 6 or 12 months before enrollment or the presence of symptomatic disease (15, 17, 20). However, the definition of progressive disease in studies requiring disease progression for entry was either unclear or evaluated individually by each investigator in a multicenter trial (15, 17). The typically slow progression of even refractory thyroid cancer can make documentation of disease progression challenging. The current trial used a simple objective criterion for entry, namely, the presence of at least one FDG-PET–avid lesion with uptake clearly above blood-pool background. Although the entry criteria for this study may not be directly comparable to prior studies of other TKIs in thyroid cancer, the presence of FDG-avid tumors is strongly predictive of a more aggressive course of the disease and associated with a 5-year OS of less than 50% (4). Tumors were highly metabolically active by FDG-PET, with median lesion SUV of 7.9, indicating an aggressive phenotype.

As in some prior published studies, we included patients with iodine-refractory WDTC and MTC, diseases for which there are few, if any, accepted systemic therapy choices. Although we reported results from both cancers combined, the RECIST response rates were similar (WDTC, 28%; MTC, 50%), and sunitinib clearly had activity in both tumor types. Although it is not possible to directly compare results from the current trial with those previously published, therapy with continuous sunitinib was associated with a high rate of disease control. Seventy-seven percent of patients had no evidence of disease progression 3 months after trial initiation. The median TTP was 12.8 months and the median survival has not been reached. These results seem to compare favorably with what would be expected in this population with FGD-PET–avid tumors (4). Furthermore, 78% of patients had some degree of tumor reduction. This is very important as patients with stable
uptake could be an early indicator of response in other diseases, based on data showing that a decline in FDG uptake 1 week after therapy initiation with subsequent response in MTC had a significant decrease from baseline levels. In addition, in those patients with measurable serum tumor markers, 58% of patients with WDTC and 50% with MTC had a significant decrease from baseline levels.

We attempted to correlate the results of a FDG-PET scan 1 week after therapy initiation with subsequent response to therapy, based on data showing that a decline in FDG uptake could be an early indicator of response in other diseases per RECIST represent a heterogeneous group, which includes patients with a 29% reduction and a 19% increase in tumor size. Radiological response and disease control were seen both in WDTC and in MTC. In addition, in those patients with measurable serum tumor markers, 58% of patients with WDTC and 50% with MTC had a significant decrease from baseline levels.

In conclusion, continuous oral administration of sunitinib was effective in patients with iodine-refractory WDTC and MTC. Gastrointestinal bleeding and hemoptysis were the most serious complications of therapy and may

### Table 3. Summary of treatment-related adverse events

<table>
<thead>
<tr>
<th>Category</th>
<th>Total n (%)</th>
<th>Grade ≥3 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (26)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>2 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>2 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (26)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>3 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Dysphagia</td>
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<td>Odynophagia</td>
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<td>1 (3)</td>
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<tr>
<td>GI bleed</td>
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<td>2 (1 grade 5)</td>
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<tr>
<td>Dermatologic</td>
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</tr>
<tr>
<td>Hand/foot syndrome</td>
<td>9 (26)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Pulmonary</td>
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<tr>
<td>Hemoptyis</td>
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</tr>
<tr>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Supraventricular tachycardia</td>
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<tr>
<td>Hematologic</td>
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<tr>
<td>Leukopenia</td>
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<td>Neutropenia</td>
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<tr>
<td>Anemia</td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>ENT</td>
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<tr>
<td>Epistaxis</td>
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<tr>
<td>Edema of larynx</td>
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<td>Endocrine</td>
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<td>Hypocalcemia</td>
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<tr>
<td>Neurologic</td>
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<td>Peripheral neuropathy</td>
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<tr>
<td>Infection</td>
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<td>1 (3)</td>
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</table>

**NOTE:** Grades 3 and higher are reported in a separate column.

**Abbreviations:** GI, gastrointestinal; ENT, ear, nose, and throat.
be associated with the use of anticoagulation. Multitargeted TKIs have changed the therapy of WDTC and MTC. Although phase III clinical trials are necessary to define their precise clinical benefit, phase II trials conducted to date show a toxicity profile favorable to that of cytotoxic chemotherapy, with more consistent response rates and response duration.

Disclosure of Potential Conflicts of Interest

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References


Table 4. Comparison to other trials of TKI for thyroid cancer

<table>
<thead>
<tr>
<th>Study medication</th>
<th>Response rate (%)</th>
<th>Progression-free survival (mo)</th>
<th>Median survival (mo)</th>
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<td>Sunitinib*</td>
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<td>Sorafenib (18)</td>
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<td>23/37.5†</td>
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<td>Motesanib (15)</td>
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<tr>
<td>Motesanib (20)†</td>
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<td>11</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviation: NR, not reached.
*Current study.
†The study had two arms with different inclusion criteria.
‡The study only included patients with medullary carcinoma.

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Phase II Study of Daily Sunitinib in FDG-PET–Positive, Iodine-Refractory Differentiated Thyroid Cancer and Metastatic Medullary Carcinoma of the Thyroid with Functional Imaging Correlation

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