Biomarkers as Predictors of Response to Treatment with Motesanib in Patients with Progressive Advanced Thyroid Cancer

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Context: Antiangiogenic therapies have shown potential in the treatment of advanced thyroid cancer, but it is uncertain which patients are most likely to benefit from therapy.

Objective: This prespecified exploratory analysis investigated whether baseline levels and/or changes in circulating biomarkers could predict tumor response and/or progression-free survival (PFS) among patients enrolled in a phase 2 study of motesanib in advanced thyroid cancer.

Design/Setting/Patients: Patients with progressive locally advanced or metastatic medullary or differentiated thyroid cancer received motesanib 125 mg once daily for up to 48 wk in a phase 2 interventional study. Samples for assessment of circulating biomarkers of angiogenesis or apoptosis were collected at study wk 1 (baseline), 2, 4, 8, 16, 24, 32, 40, 48, and 4 wk after cessation of motesanib treatment. Tumor response was assessed per Response Evaluation Criteria in Solid Tumors by independent review.

Results: Change from baseline in serum placental growth factor (PlGF) after 1 wk of treatment correlated with best tumor response (Kendall rank correlation, 0.28; $P < 0.0001$). Using a Fisher exact test, the most significant separation between patients who had an objective response and those who did not was at a 4.7-fold increase in PlGF. The response rate among patients with a greater than 4.7-fold increase in PlGF was 30% compared with 3% below this threshold. There was also a significant separation between responders and nonresponders at a 1.6-fold decrease in soluble vascular endothelial growth factor (VEGF) receptor 2 after 3 wk of treatment. Patients with baseline serum VEGF less than 671 pg/ml had significantly longer PFS times than the remainder of patients.

Conclusions: Changes in PlGF and soluble VEGF receptor 2 levels after initiation of therapy predicted response to motesanib in patients with advanced differentiated thyroid cancer or metastatic medullary thyroid cancer. Lower baseline VEGF levels were associated with longer PFS. (***J Clin Endocrinol Metab* 95: 5018–5027, 2010**)

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Abbreviations: Ang, Angiopoietin; CI, confidence interval; DTC, differentiated thyroid cancer; MTC, medullary thyroid cancer; PFS, progression-free survival; PlGF, placental growth factor; PR, partial responses; RECIST, Response Evaluation Criteria in Solid Tumors; sKit, soluble Kit; sVCAM, soluble vascular cell adhesion molecule; sVEGFR, soluble VEGFR; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Progressive or advanced medullary (MTC) and differentiated thyroid cancers (DTC) remain difficult to treat (1, 2). Recently therapies that inhibit angiogenic signaling pathways have emerged as potentially effective treatment options (3–11). However, many of these agents inhibit more than one pathway in a complex network, and not all patients respond to treatment. Assessment of circulating levels of angiogenic cytokines and other biomarkers may help identify patients most likely to benefit from these therapies (12–18).

Increased serum levels of vascular endothelial growth factor (VEGF) are characteristic of DTC (19, 20) and have been associated with greater tumor growth and progression as well as shorter recurrence-free survival (21–23). Although dysregulated signaling by the tyrosine kinase Ret has been implicated as a critical pathophysiological pathway in MTC (24, 25), VEGF expression is elevated in 50% of some primary MTCs and in 75% of its metastases compared with normal thyroid tissues (19). A number of recent studies have suggested that agents inhibiting the VEGF signaling pathway may have activity in the treatment of advanced thyroid cancer (5, 7–11). Clinical benefits associated with such therapies have been reported among patients with DTC and patients with MTC (5, 7–9), suggesting that the VEGF signaling pathway may play a more significant role in MTC than traditionally thought. However, response to such treatments varies greatly among patients, and biomarkers that may indicate which patients are most likely to benefit from therapy with VEGF pathway inhibitors have not yet been identified.

Motesanib is an orally administered small-molecule antagonist of VEGF receptors (VEGFRs) 1, 2, and 3; Kit; and platelet-derived growth factor receptor (26). In a phase 2 study among patients with progressive advanced DTC or MTC, treatment with motesanib was tolerable and showed signs of clinical benefit in DTC patients and disease control in MTC patients (3, 6).

Here we report results from a planned subanalysis of the motesanib thyroid cancer study that investigated whether baseline levels and/or changes in specific biomarkers were associated with tumor response and/or progression-free survival (PFS) during motesanib treatment in patients with progressive advanced DTC or MTC. We assessed biomarkers that are direct indicators of motesanib biological activity or may reflect the effects of motesanib on the vasculature and/or apoptosis.

Patients and Methods

Patients

Eligible adult patients had histologically confirmed locally advanced or metastatic DTC or MTC and documented evidence of disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) (27) within 6 months of study entry or (MTC patients only) disease symptoms (diarrhea and/or flushing) at the time of enrollment. Complete eligibility criteria have been previously published (3, 6). The study protocol received approval from each site's independent ethics committee or institutional review board. Each patient provided written informed consent.

Study design and treatment

This was a single-arm, phase 2, open-label, multicenter study. Patients with DTC and MTC were enrolled into two prospectively defined cohorts. Patients self-administered motesanib (Amgen Inc., Thousand Oaks, CA) 125 mg orally once daily following protocol-specified dosing rules (3, 6) for up to 48 wk or until disease progression or unacceptable toxicity occurred. Tumor response was assessed per modified RECIST (27) by an independent central review as previously described (3, 6). The primary end point was the objective response rate per RECIST as assessed by independent central review. Secondary end points included PFS, overall survival, pharmacokinetics, and safety (3, 6). The primary objective of this prospectively defined biomarker subanalysis was to correlate changes in angiogenic and apoptotic markers with tumor response and identify potential associations between baseline biomarker levels, PFS, and tumor response.

Sample collection

Serum and plasma samples were collected before motesanib administration on the first day of study wk 1 and on the first day of wk 2, 4, 8, 16, 24, 32, 40, and 48. An end-of-study sample was collected 4 wk after the last dose of motesanib. Samples were stored at −80 C until analysis.

Biomarker analysis

Serum and plasma biomarkers were analyzed by sandwich ELISA and an electrochemiluminescent multiplexed sandwich immunoassay (Meso-Scale Discovery, Gaithersburg, MD). Levels of soluble VEGFR (sVEGFR)-1, placental growth factor (PlGF), VEGF, and basic fibroblast growth factor were measured in a single sample using a four-plex Meso-Scale Discovery assay kit according to the manufacturer's instructions. Assay performance characteristics were evaluated following specific procedures, a portion of which have been reported previously (28). Results for basic fibroblast growth factor are not reported because 80% of the samples were below the lower limit of quantitation. Soluble Kit (sKit) and sVEGFR2 were measured in a single sample using a two-plex Meso-Scale Discovery assay following the same performance characteristics evaluation. Electrochemiluminescence was detected using an Meso-Scale Discovery Sector Imager 6000. Soluble vascular cell adhesion molecule (sVCAM)-1, angiopoietin (Ang)-1, and Ang2 were measured by sandwich ELISA using commercially available antibodies (R&D Systems, Minneapolis, MN). Color development was measured using a SpectraMax Plus 384 spectrophotometer (Molecular Devices, Sunnyvale, CA). Samples were analyzed in triplicate, and biomarkers were quantitated by interpolation from a standard curve run on each microtiter plate.

Serum caspase-3/7 enzyme activity was measured using a quasiquantitative luminescence assay (Caspase-GLO; Promega, Madison, WI) and an EnVision model 2101 plate reader

(PerkinElmer, Waltham, MA). Samples were quantitated relative to a normal human serum control (BRH77486; Bioreclamation, Hicksville, NY) on each plate.

Statistical analysis

Patients with a baseline and at least one postbaseline blood sample were included in the analysis set. Data obtained from samples collected on d 1 before the first motesanib dose were considered baseline values. Samples were not pooled, and each sample was assayed once for each biomarker. Samples below the lower limit of quantitation were excluded from the analysis. To achieve a normal distribution, biomarker concentration values were log transformed before statistical analysis (except for caspase activity values, which were normally distributed). Statistical significance was determined from the regression analysis using an F test. *P* values were not corrected for multiple comparisons; however, a significance threshold of 0.01 was used to guard against false discovery. The Fisher exact test was performed to identify biomarker levels or changes therein that defined the most significant separation between responders and nonresponders. Biomarker levels were correlated to tumor response (percentage change in sum of the longest diameters of target lesions) using the Kendall rank correlation. Comparisons between PFS and tumor response groups were made using a Cox proportional hazards model. PFS was the time from initiation of treatment to the date of disease progression or death (3, 6). The clinical treatment of patients, assessment of response [per RECIST (27) by independent central review], analysis of biomarker concentrations in serum and plasma, and statistical analyses were performed by separate groups that worked independently of one another.

Results

Patients

A total of 184 patients (DTC, n = 93; MTC, n = 91) were enrolled in the phase 2 study and received one or more doses of motesanib (Table 1). As reported previously (3, 6), most patients had metastatic disease (DTC, 99%; MTC, 93%) and had received prior therapy for thyroid cancer. The median age was 62 yr in the DTC cohort and 49 yr in the MTC cohort. The median lengths of treatment were 35 wk for the DTC cohort and 38 wk for the MTC cohort. The biomarker and caspase activity analysis included serum samples from 178 patients and plasma samples from 172 patients.

The objective response rate was 14% in the DTC cohort and 2% in the MTC cohort [all confirmed partial responses (PR)] (3, 6). Forty-eight percent of MTC patients achieved durable (≥24 wk) stable disease and 76% had a decrease from baseline in tumor dimensions. Median PFS for patients in the DTC and MTC cohorts was 40 wk [95% confidnce interval (CI) 32–50] and 48 wk (95% CI 43–56), respectively. Results from the primary analysis of the study have been reported previously (3, 6).

TABLE 1. Key patient demographics and baseline characteristics

Characteristic	DTC (n = 93)	MTC (n = 91)
Sex, n (%)		
Women	44 (47)	32 (35)
Men	49 (53)	59 (65)
Median age, yr (range)	62 (36–81)	49 (18–77)
Race/ethnicity, n (%)		
White	85 (91)	86 (95)
Hispanic/Latino	3 (3)	4 (4)
Asian	4 (4)	1 (1)
Black	1 (1)	0 (0)
Median time since initial diagnosis, yr (range)	4.4 (0.4–21.3)	6.2 (0.2–25.4)
Disease extent, n (%)		
Metastatic	92 (99)	85 (93)
Locally advanced	1 (1)	5 (5)
Number of sites of disease, n (%)		
0	0 (0)	1 (1)
1	26 (28)	8 (9)
2	39 (42)	22 (24)
3 or more	28 (30)	60 (66)
ECOG performance status, n (%)		
0	47 (51)	39 (43)
1	37 (40)	42 (46)
2	9 (10)	9 (10)
3	0 (0)	1 (1)
Prior therapy (for thyroid cancer), n (%)		
Thyroidectomy	93 (100)	N/A
External beam radiation therapy		
0 unique sites	40 (43)	45 (49)
1 unique site	32 (34)	26 (29)
2 or more unique sites	21 (23)	20 (22)
Radioiodine therapy		
0 courses	3 (3)	78 (86)
1 course	14 (15)	11 (12)
2 or more courses	76 (82)	2 (2)
Chemotherapy		
0 regimens	77 (83)	58 (64)
1 regimen	10 (11)	19 (21)
2 or more regimens	6 (6)	14 (15)
Median time since last therapy, months (range)	11.6 (1.2–367.2)	11.4 (0.4–232.7)

ECOG, Eastern Cooperative Oncology Group; N/A, not applicable.

Pharmacodynamics of biomarkers during motesanib treatment

After 1 wk of motesanib treatment, mean serum PlGF levels increased significantly from baseline in both cohorts (DTC, 3.75-fold, $P < 0.0001$; MTC, 2.6-fold, $P < 0.0001$). Plasma PlGF levels showed a similar increase

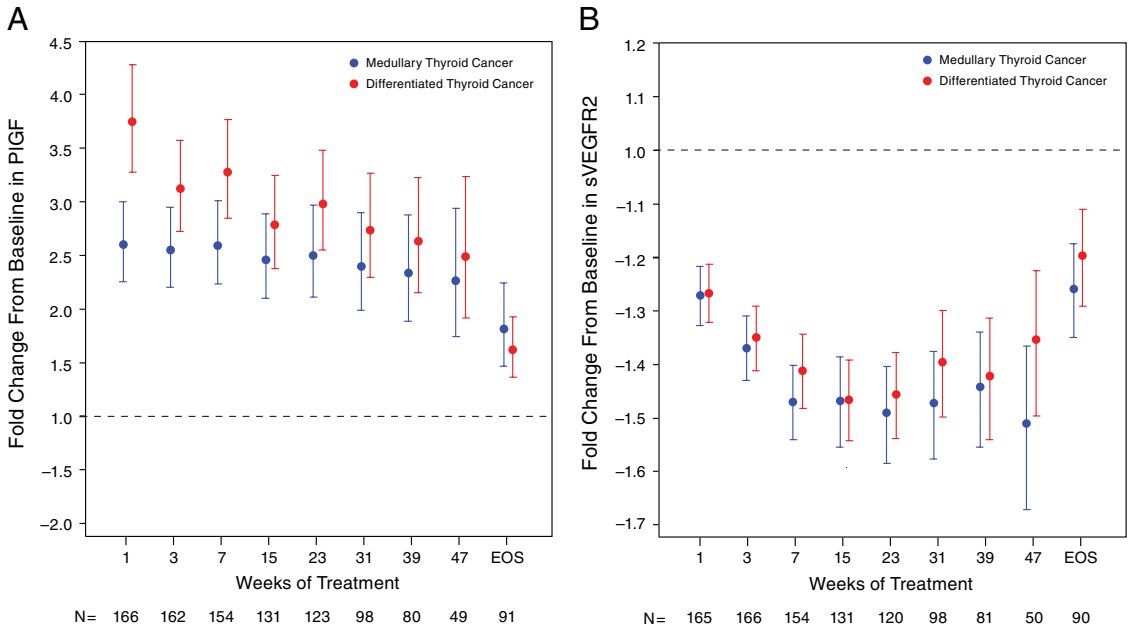

FIG. 1. Mean fold change (±95% CI) from baseline in serum PlGF (A) and sVEGFR2 (B) in MTC and DTC cohorts during motesanib treatment. Exact, statistically significant fold changes from baseline are shown for selected time points. N, Number of serum samples with measurable analyte; EOS, end of study.

over the same time period (DTC, 3.7-fold, $P < 0.0001$; MTC, 2.6-fold, $P < 0.0001$). The increase in PlGF was more marked in DTC patients, particularly over the first 7 wk of treatment (Fig. 1A). Similarly, exposure to motesanib was greater in the DTC cohort than in the MTC cohort. The mean wk 1 area under the concentration *vs.* time curve (0–inf) was 4.69 mg · h/ml for DTC patients compared with 2.16 mg · h/ml for MTC patients. At the end of the study visit, PlGF concentrations had decreased toward baseline.

In both cohorts serum sVEGFR2 progressively decreased from baseline during the first 23 wk of treatment (DTC, 1.48-fold decrease at wk 8, $P < 0.0001$; MTC, 1.40-fold decrease at wk 8, $P < 0.0001$) and then remained relatively stable (Fig. 1B). Serum sVEGFR2 concentrations appeared to be returning toward baseline at the end of the study visit (average of 1.23-fold decrease from baseline across both cohorts; $P < 0.0001$). Plasma sVEGFR2 levels displayed similar changes (data not shown).

Serum VEGF increased modestly in both cohorts throughout the study, with the greatest increase from baseline observed after 1 wk of motesanib treatment (DTC, 1.46-fold, $P < 0.0001$; MTC, 1.20-fold, $P < 0.0001$; Fig. 2A). Increases in plasma VEGF after 1 wk of treatment were slightly larger (1.76-fold change across both cohorts; $P < 0.0001$) but then slowly decreased to approximately 1.28-fold above baseline ($P = 0.003$), which was maintained through the remainder of the study (data not shown).

All other biomarkers measured in this study also showed varying responses to motesanib treatment (Fig. 2, B–G). Serum levels either consistently increased (sVCAM-1, caspase-3/7 activity) or decreased across cohorts (sKit, Ang2) or showed cohort-specific changes. Levels of serum sVEGFR1 and Ang1 decreased after 15 and 31 wk of treatment, respectively, but only in the MTC cohort. Serum sVEGFR1 was increased above baseline in both DTC and MTC patients at the end-of-study visit. No change in Ang1 was observed in DTC patients. Results obtained for plasma sVEGFR1, sKit, and Ang2 were consistent with those observed with serum samples (data not shown). The assay for Ang1 was not qualified for the analysis of plasma samples.

Association between changes in biomarkers and tumor response

Across patients in both the DTC and MTC cohorts, changes in serum PlGF as early as 1 wk of treatment correlated with best tumor response (as assessed by RECIST and independent central review; Kendall rank correlation 0.28; $P < 0.0001$). Using the Fisher exact test, the most significant separation between patients who had a PR and those who did not was at a 4.7-fold increase from baseline in PlGF levels (Fig. 3A). Patients with a greater than 4.7-fold increase in PlGF after 1 wk of treatment were more likely to achieve a PR during the study period than those with a less than 4.7-fold increase. Of 139 patients in the study who had an assessment of serum PlGF after 1 wk of treatment and imaging for assessment of response during the study, 37 (27%) had a greater than 4.7-fold increase in PlGF; of those, 11 (30%) had a PR during the study period (Fig. 4A). The

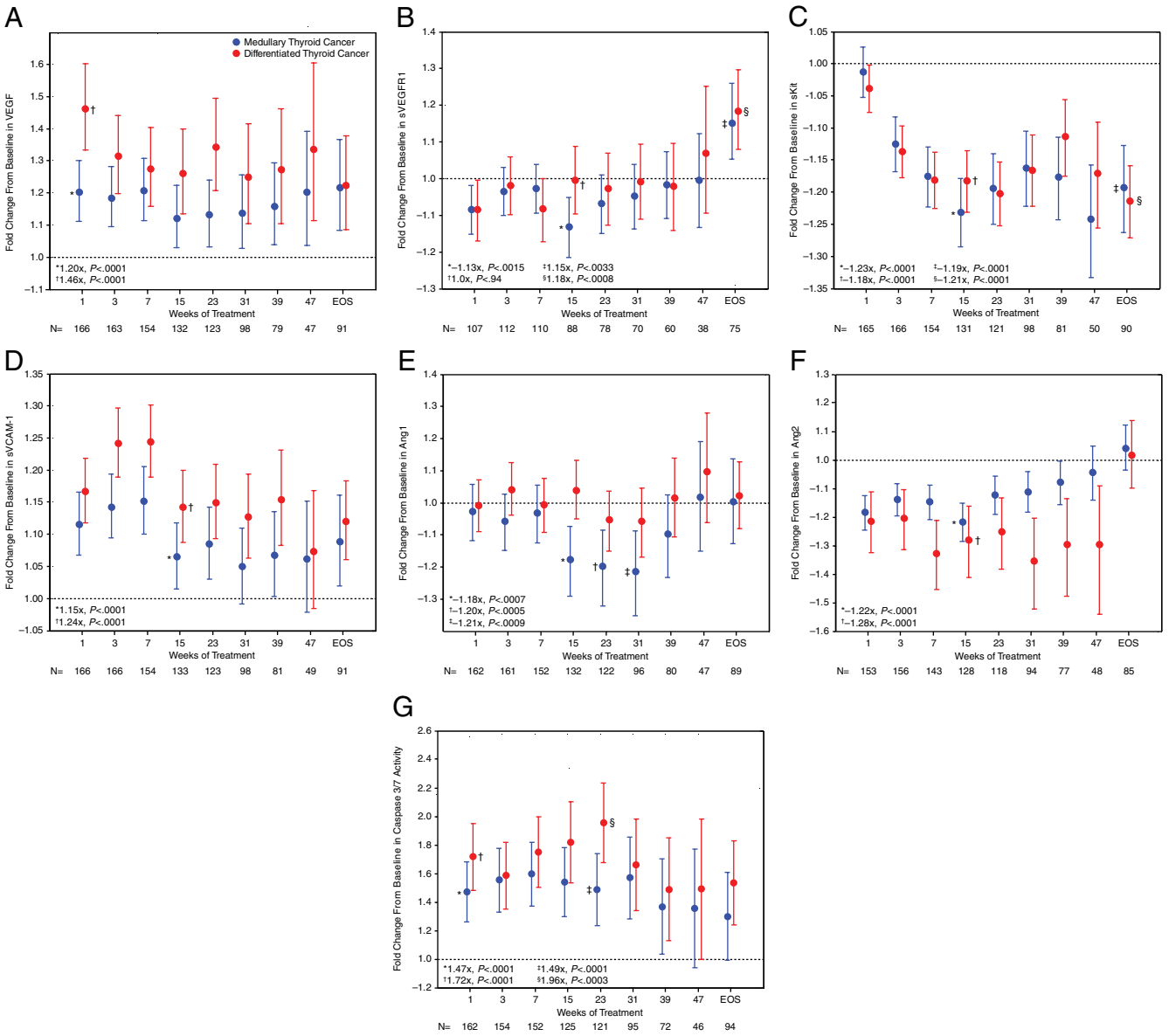

FIG. 2. Mean fold change (±95% CI) from baseline in serum VEGF (A), sVEGFR1 (B), sKit (C), sVCAM-1 (D), Ang1 (E), Ang2 (F), and caspase-3/7 (G) activity in patients with MTC or DTC during motesanib treatment. Exact, statistically significant fold changes from baseline are shown for selected time points. N, Number of serum samples with measurable analyte; EOS, end of study.

remaining 102 patients (73%) had a less than 4.7-fold increase in PlGF; of those, only three (3%) achieved a PR during the study period (Fig. 4B). Significant separations between responders and nonresponders were observed at cutoffs between 2.5- and 8.4-fold changes from baseline in PlGF (data not shown). Changes in PlGF also correlated with tumor response after 3 wk of treatment (Kendall rank correlation 0.33; $P < 0.0001$). The best separation between responders and nonresponders was at a 5.3-fold change from baseline in PlGF.

There were also correlations between the fold decrease from baseline in sVEGFR2 during the first 3 wk of treatment and best tumor response (Kendall rank correlation −0.23; $P = 0.0006$) and between changes in caspase-3/7 activity and tumor response (Kendall rank correlation 0.29; $P < 0.0001$). Using a Fisher exact test, greatest separation between responders and nonresponders was at a −1.6-fold change in sVEGFR2 (Fig. 3B). Of 165 patients with assessments of serum sVEGFR2 and tumor response at wk 4, 24 had a less than −1.6-fold change in sVEGFR2; of those, seven (28%) had a PR per RECIST ($P = 0.0003$). Similarly, a 2.1-fold change from baseline in caspase-3/7 activity separated responders from nonresponders (Fig. 3C). Of 141 patients with assessments of serum caspase-3/7 activity and tumor response, 23 had a greater than 2.1-fold change in caspase-3/7 activity; of those, nine (39%) had a PR per RECIST ($P < 0.0001$).

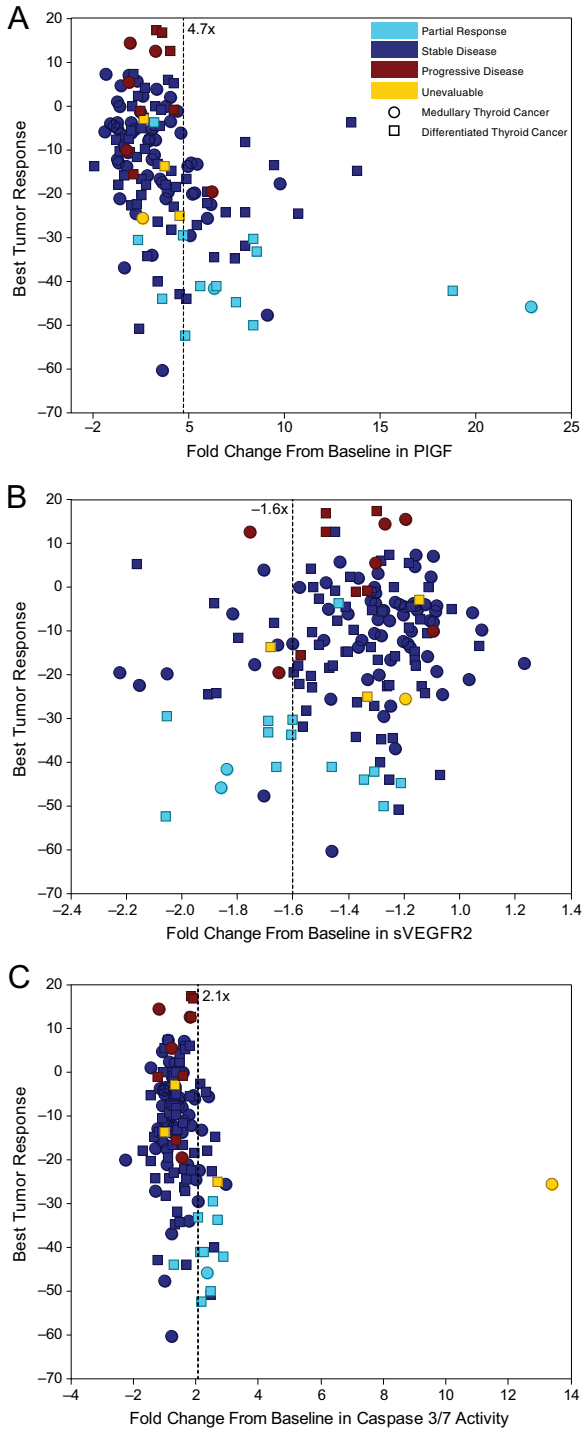

FIG. 3. Association between best tumor response (by RECIST and independent central review) and change from baseline in serum PlGF (A) after 1 wk of treatment, sVEGFR2 after 3 wk (B), and caspase-3/7 after 3 wk (C). The *dashed line* marks the most significant separation between responders and nonresponders (χ^2 analysis).

No significant correlations were found between tumor response and changes in levels of VEGF, sVEGFR1, sKit, sVCAM-1, Ang1, and Ang2. Combinations of biomarkers did not have a better correlation to tumor response than individual biomarkers (data not shown).

Association between baseline biomarker levels and disease progression and tumor response

Across patients in both cohorts, baseline serum PlGF levels did not predict either PFS or PR. However, lower baseline levels of VEGF defined a population of patients who had a better prognosis. Patients with a baseline serum VEGF level of less than 671 pg/ml had significantly better PFS (by 179 d) than patients with a baseline level of greater than 671 pg/ml (Cox proportional hazards model, $P = 0.0007$; Fig. 5). In a random permutation test (n = 1000), results with this level of significance were achieved in 2.1% of cases. Lower baseline VEGF levels were not, however, predictive of a tumor response during motesanib treatment. The proportion of patients in the two groups was similar: 11 and 10% in the less than 671 pg/ml and greater than 671 pg/ml groups, respectively.

Discussion

This is the first study to evaluate a broad panel of circulating biomarkers for the prediction of clinical outcomes among patients receiving antiangiogenic therapy for advanced thyroid cancer. In both DTC and MTC cohorts, all tested biomarkers responded to motesanib treatment with specific patterns of temporal increases or decreases in their respective levels. Except for sVEGFR1 and Ang1, the direction of change was generally the same in both cohorts. As expected, levels of biomarkers that are direct motesanib targets (sKit, sVEGFR2) or their ligands (PlGF, VEGF) changed early in the study. The results suggest that the observed alterations in the tested biomarkers may be surrogate markers of inhibition of the kinase activity of motesanib's molecular targets or of indirect effects of that inhibition.

Changes in serum PlGF and sVEGFR2 in response to motesanib treatment have previously been reported among patients with solid tumors (29). In that study, the range of exposure to motesanib was much greater and significant associations between change in PlGF and sVEGFR2 and area under thecurve were observed. In the phase 2 thyroid cancer study, exposure to motesanib in the DTC cohort was greater than in the MTC cohort (see *Results*) (3, 6), suggesting that the more pronounced change in serum PlGF observed in DTC patients may be the result of greater exposure to motesanib in that cohort.

Associations between clinical outcomes and PlGF, sVEGFR2, VEGF, and caspase-3/7 activity (a measure of apoptosis) were observed. Changes, but not baseline levels, of serum PlGF, sVEGFR2, and caspase-3/7 activity occurring shortly after initiation of motesanib treatment predicted subsequent objective response. Although the exact physiological role of PlGF is uncertain, it is an impor-

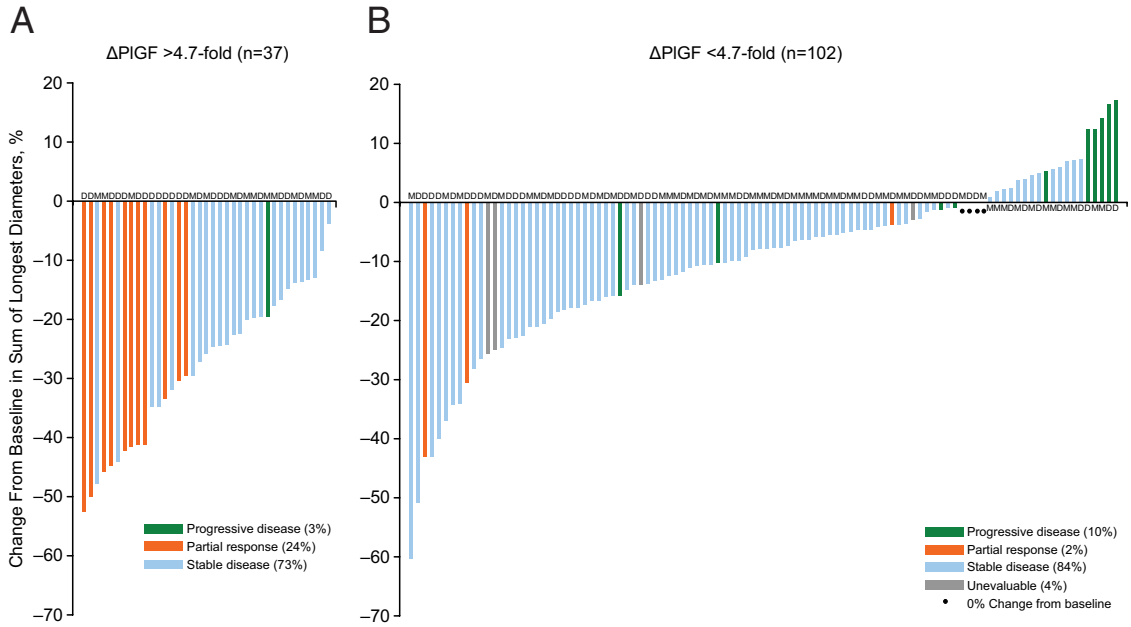

FIG. 4. Best tumor response in patients with DTC or MTC stratified according to change from baseline in serum PlGF of greater than 4.7-fold increase (A) or less than 4.7-fold increase (B) as determined by χ^2 analysis. D, Differentiated thyroid cancer; M, medullary thyroid cancer.

tant mediator of growth and neovascularization of tumors (30, 31). Down-regulation of PlGF (and concurrent up-regulation of VEGF) has been observed in thyroid tumor biopsies (32), suggesting the presence of a PlGF-VEGF signaling mechanism in thyroid cancer. Similarly, the physiological role of sVEGFR2 is presently unknown, although membrane-bound VEGFR2 is the key mediator of the proangiogenic effects of VEGF-A (33). The increase in PlGF and VEGF and the decrease in sVEGFR2 (which may act as a decoy receptor) may be due to a homeostatic response to inhibition of proangiogenic signaling. Reducing expression of the decoy receptor while increasing PlGF and VEGF may be an attempt to increase the level of proangiogenic signaling. The similarity in the sVEGFR2 response observed in the MTC and DTC cohorts suggests that exposure is not the sole determinant of changes in biomarker concentrations. Although few biomarker studies have assessed caspase-3/7 activity, pharmacodynamic responses have been demonstrated in a study examining an apoptosis-inducing agent (34).

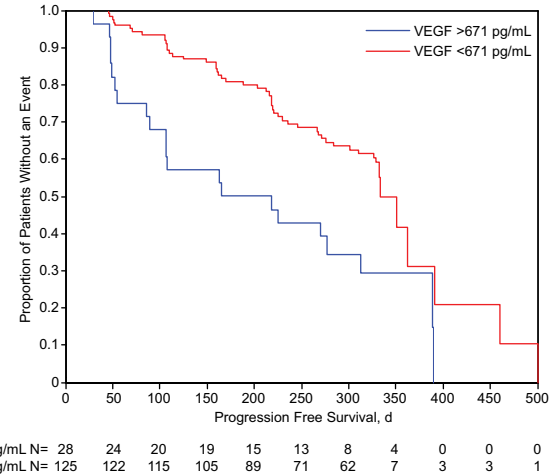

FIG. 5. PFS in patients with DTC and MTC stratified by low (*red lines*) or high (*blue lines*) baseline levels of serum VEGF (A) or sVCAM-1 (B).

Baseline serum levels of VEGF were prognostic for PFS. Elevated VEGF-A expression occurs frequently in both MTC and DTC (19, 20) and has been associated with increased local and distant recurrence and reduced recurrence-free survival (21–23). The observed association between baseline VEGF levels and poorer PFS in this study may reflect more aggressive disease. No association between baseline levels of any biomarker (including serum VEGF) and objective response was shown in this study. The data suggest that changes in different biomarkers may predict objective response to therapy, whereas baseline levels of VEGF are prognostic for PFS.

Temporal changes in PlGF and/or sVEGFR2 might be useful in identifying thyroid cancer patients most likely to respond to motesanib therapy and appear to be better predictors of response than baseline levels. Although the best separation between responders and nonresponders was observed at a 4.7-fold change in PlGF, a range of possible cutoffs in biomarker changes could be used to select a population more likely to respond. In this study, cutoffs from 2.5- to 8.4-fold change from baseline in PlGF yielded significant separations. The minimum cutoff that could have practical utility is an approximately 2-fold change: in a chemotherapy-treated cancer population (n = 62) (35), the intrapersonal variation in PlGF was less than 1.8-fold (Amgen Inc., unpublished data). Lower cutoffs

are more inclusive for patients, whereas excluding those are unlikely to achieve an objective response.

Changes in plasma VEGF, sVEGFR2, sVEGFR3, and sKit have previously been described in patients with advanced thyroid cancer (any type) receiving axitinib (8). However, correlations between changes in sVEGFR2 and outcomes were not assessed. Biomarker responses to treatment with VEGF(R) pathway inhibitors have also been conducted in other tumor types (12–14, 16–18, 36), but few have investigated associations with outcomes (14, 16, 18, 37). Recently a study in patients with early-stage non-small cell lung cancer who received the VEGFR inhibitor pazopanib has shown that baseline levels of, but not changes in, PlGF correlated with tumor response (38). In a study of neoadjuvant treatment with bevacizumab in colorectal cancer, patients with a greater than 2-fold change in PlGF had minimal disease at surgery (37). Among renal cell carcinoma patients receiving sunitinib, those who achieved PR or stable disease had greater changes in VEGF, sVEGFR2, and sVEGFR3 than those who did not respond to treatment (14).

Results from clinical studies showing that thyroid cancers are sensitive to antiangiogenic therapies targeting the VEGF signaling pathway have opened the potential for new therapeutic avenues in this disease (5, 7–11). The observation that changes in circulating biomarkers qualitatively similar to those measured in the present study have also been reported with other VEGF pathway inhibitors raises the possibility that they may have broader applicability. The ability to identify patients with thyroid cancer most likely to respond to such treatments would be of immediate clinical importance because the current National Comprehensive Cancer Network treatment guidelines suggest that treatment with small-molecule tyrosine kinase inhibitors (such as sorafenib and sunitinib) should be considered for some patients with progressive disease for whom clinical trials are either unavailable or not appropriate (39).

However, a number of challenges remain if the biomarkers identified in this study are to have clinical application. In particular, larger prospective randomized studies will be necessary to independently validate the predictive and/or prognostic value of these biomarkers and to determine the most appropriate time point(s) for assessment. Additionally, the associations between biomarkers and tumor response and PFS are based on RECIST assessments (27). Recent studies have suggested that these criteria may have limitations when determining the effects of antiangiogenic agents on tumor volume (40, 41). Demonstration of an association between the biomarkers we identified and overall survival would provide much stronger evidence for the potential clinical utility of these biomarkers. Furthermore, the mechanism(s) by which VEGFR inhibitors mediate the observed alterations in biomarkers is uncertain. Changes may be due to either direct effects of motesanib on the tumor or to a physiological response to drug exposure, which may be indicative only of better pharmacokinetics. Administration of sunitinib (42) or motesanib (Amgen Inc., data on file) in normal mice results in increased PlGF.

In summary, the changes in PlGF and sVEGFR2 levels occurring early after the initiation of therapy predicted response to motesanib in patients with advanced DTC and MTC, whereas baseline VEGF was prognostic for PFS. This is the first report describing the potentially predictive value of the changes in the biomarker levels for anti-VEGFR therapy in thyroid cancer. An independent validation in prospective randomized studies is needed to confirm these results.

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