Sorafenib has clinical activity against metastatic papillary thyroid cancer but requires close monitoring and aggressive management of drug toxicity

Kloos RT, Ringel MD, Knopp MV, Hall NC, King M, Stevens R, Liang J, Wakely PE Jr, Vasko VV, Saji M, Rittenberry J, Wei L, Arbogast D, Collamore M, Wright JJ, Grever M, Shah MH. Phase II trial of sorafenib in metastatic thyroid cancer. J Clin Oncol 2009;27:1675-84.

SUMMARY

BACKGROUND This phase II clinical trial of sorafenib is based on the central role of the Ras-Raf-MAP-ERK signaling pathway and vascular endothelial growth factor (VEGF) in papillary thyroid cancer (PTC). Although sorafenib was initially considered to be a selective RAF kinase inhibitor, it is now known to be a multikinase inhibitor that targets several receptor tyrosine kinases at submicromolar concentrations, including VEGF receptors (VEGFRs) 1 to 3 and platelet-derived growth factor receptor.

METHODS The primary end point of the study was the objective response rate. Secondary end points were the correlation of serum thyroglobulin (Tg), functional imaging, tumor genotype, and signaling inhibition in tumor biopsies. The study used a Simon minimax two-stage design. In a typical two-stage design of a phase II clinical trial of cancer, a fixed number of patients are initially enrolled. The trial may be terminated for lack of therapeutic efficacy if the number of treatment successes after the first stage is too small. If so, an additional fixed number of patients are enrolled to accumulate additional information on efficacy. Accrual to arm B in the Kloos study was designed to stop as soon as arm A was fully accrued. The study subjects were patients who were 18 years of age or older with adequate performance status and measurable tumor. Treatment with chemotherapy or radiation therapy was not permitted within 4 weeks before entry into the study, and radioiodine therapy (with ^{131}I) was not allowed within 24 weeks before entry into the study, or within 4 weeks if the patient had a negative posttreatment ^{131}I scan. Also required were a leukocyte level ≥3000/L, an absolute neutrophil count ≥1500/L, a platelet count ≥100,000/μL, and serum bilirubin, aspartate aminotransferase and alanine aminotransferase, and creatinine levels 1.5-fold the upper limit of normal. To study the effects on tumor perfusion, dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) scans were obtained within 4 weeks before and every 8 weeks while on therapy, and fluorodeoxyglucose positron-emission tomography scans were obtained at similar time points when possible.

Patients were observed every 4 weeks for 1 year and if stable, every 12 weeks thereafter. Therapy was withheld if the patients had a grade ≥3 or recurrent grade ≥2 drug-related toxicity other than hematologic toxicity, or a grade ≥2 hand–foot–skin reaction until the toxicity resolved to grade ≤1. Sorafenib was generally tolerated; however, a dose reduction to 600 or 400 mg/day of sorafenib and a subsequent dose reescalation up to 800 mg/day was allowed. Sorafenib was continued until one of the following occurred: progressive disease, patient off sorafenib longer than 24 consecutive days for any reason, intercurrent illness that prevented further therapy, unacceptable adverse events, or patient withdrawal from the study. The response was assessed every 2 months using the Response Evaluation Criteria in Solid Tumors (RECIST) (Figure 1).

RESULTS A total of 56 patients were selected for study; 31 (55%) were men and 25 (44%) were women. The median age of the patients in arm A was 67 years (range, 33 to 90), and in arm B 56 years (range, 27 to 76). In all, 41 (73%) had PTC, 19 (46%) of whom were in arm A and 22 (54%) in arm B.

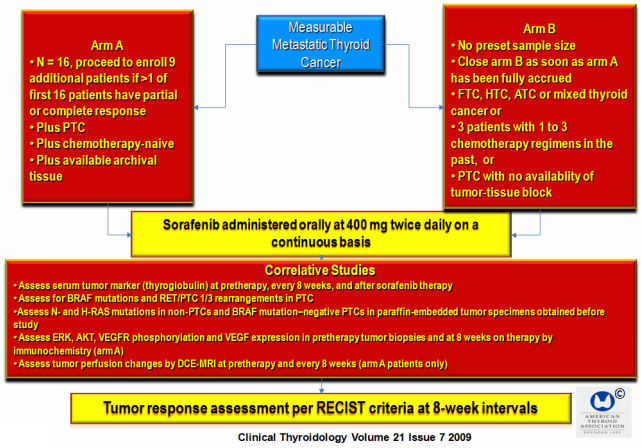

Figure 1. This figure shows the study cohort and study arms and patient demographics, and tumor histology. ATC = anaplastic thyroid cancer; DCE = dynamic contrast-enhanced; FTC = follicular thyroid cancer; HTC = Hürthle-cell cancer; MRI = magnetic resonance imaging; PTC = papillary thyroid cancer; RECIST = Response Evaluation Criteria in Solid Tumors. (Derived from data in Figure 1 of Kloos et al.)

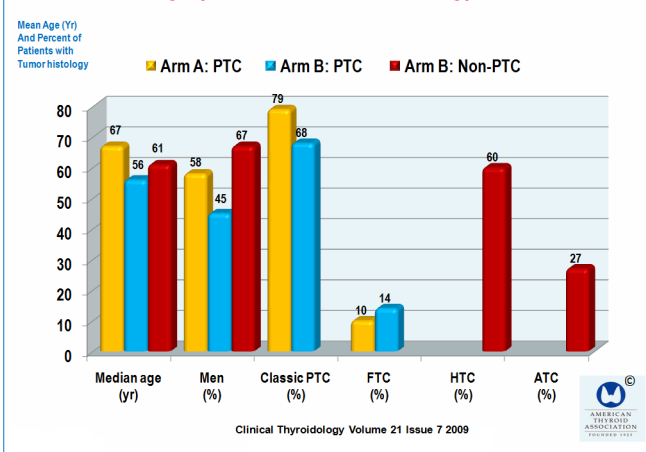

Figure 2. Patient demographics and tumor histology in arms A and B. ATC = anaplastic thyroid cancer; FTC = follicular thyroid cancer; HTC = Hürthle-cell cancer; PTC = papillary thyroid cancer. (Derived from data in Table 1 of Kloos et al.)

Thirty patients (73%) had classic PTC, 5 (12%) had follicular variant PTC, 4 (10%) had tall-cell-variant PTC, and 2 (5%) had poorly differentiated PTC. The distribution of tumor histologies in both arms of the study is shown in Figure 2. Two patients (4%) had follicular thyroid cancer (FTC), 9 (16%) had Hürthle-cell carcinoma, and 4 (7%) had anaplastic thyroid cancer. Arm A comprised 19 patients with PTC and 2 with FTC; arm B comprised 22 patients with PTC, 2 with FTC, 9 with Hürthle-cell carcinoma, and 4 with anaplastic thyroid cancer. The site of tumor metastases is shown in Figure 3.

TREATMENT ADMINISTERED The median duration of therapy was 14 months in arm A patients and 10, 8, and 2 months in patients with PTC, HTC/FTC, and ATC in arm B, respectively (Figure 4). Common grade 3 adverse events included hand–foot–skin reaction and musculoskeletal pain and fatigue. The reasons for dose reduction were hand–foot–skin reaction, diarrhea and weight loss, hypertension, fatigue, arthralgia, musculoskeletal chest pain, and mouth pain.

TUMOR RESPONSE ACCORDING TO RECIST

Of 41 patients with PTC, 6 had a partial response (PR; 15%; 95% confidence interval [CI], 6 to 29) and 23 (56%; 95% CI, 40 to 72) had stable disease for longer than 6 months. Median duration of PR was 7.5 months (range, 6 to 14). Median progression-free survival was 15 months (95% CI, 10 to 27.5) (Figures 5, 6 and 7).

BRAF mutation was detected in 17 (77%) of the 22 PTCs that were analyzed. Four of 10 paired tumor biopsies showed a reduction in VEGFR phosphorylation levels, ERK phosphorylation, and in VEGF expression during sorafenib therapy. No partial responses were noted among non-PTC patients. Clinical adverse events are shown in Figure 8.

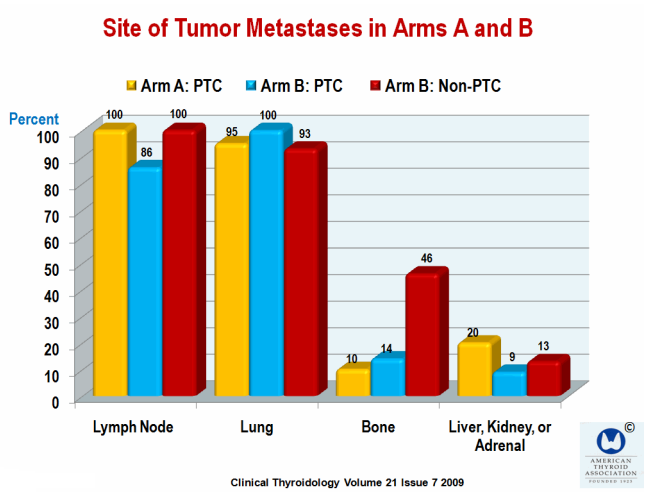

Figure 3. Site of tumor metastases in arms A and B. (Derived from data in Table 1 of Kloos et al.)

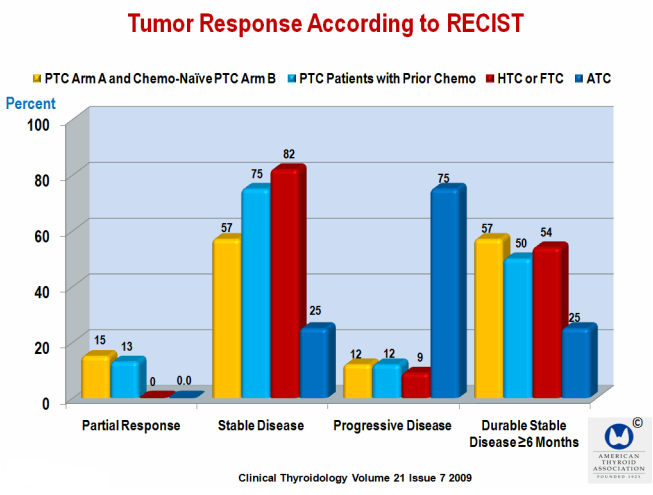

Figure 5. Tumor response is measured according to the RECIST (Response Evaluation Criteria in Solid Tumors).

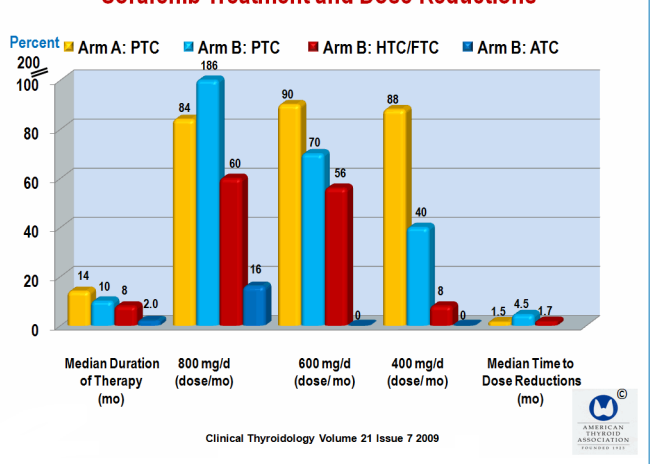

Figure 4. This is a summary of sorafenib treatment administered and the median duration of therapy and the median time to dose reductions (derived from data in Table 2 of Kloos et al.).

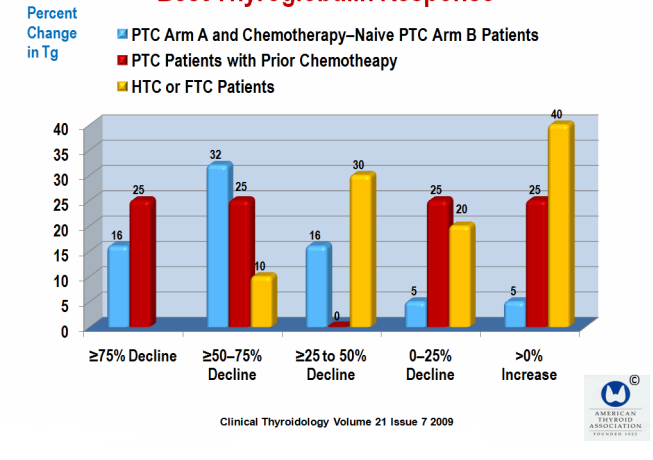

Figure 6. This shows the best thyroglobulin response to therapy.

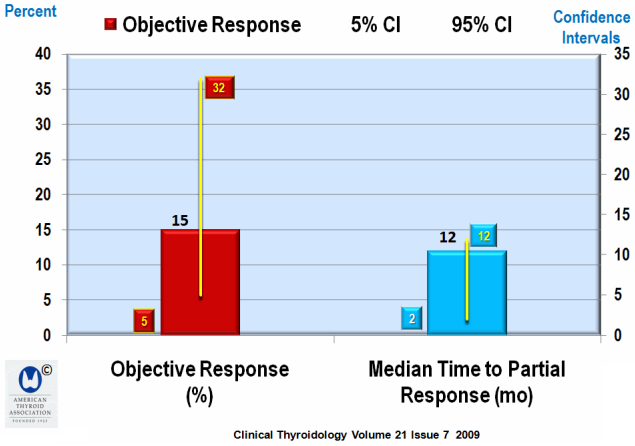

Figure 7. The objective response to sorafenib therapy is shown. Yellow bars = 5% to 95% confidence interval. The median time to partial response is shown; the top yellow flag is the 95% confidence interval (CI) and the lower left boxes are the 5% CI. The objective response (percent) and the median time to partial response (months) for sorafenib therapy is shown .

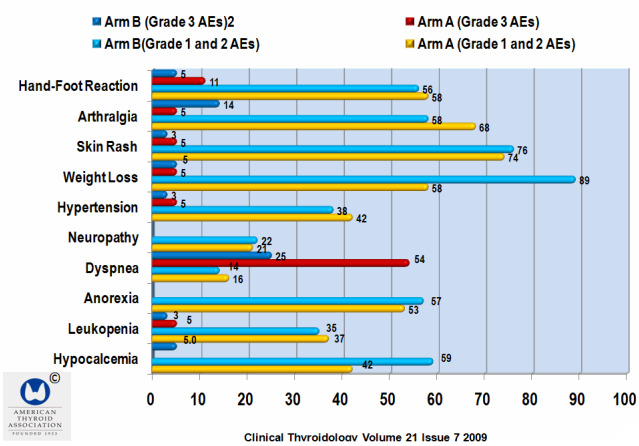

Figure 8. Some of the more common complications of sorafenib therapy. AE = adverse event.

SERUM THYROGLOBULIN CHANGES

In 14 of 18 patients (78%) the serum Tg was assessable, and declined more than 25% (Figure 6). In 10 of 14 assessable patients with PTC (71%), the 8- or 16-week DCE-MRI scans showed a median decrease of 46% (range, 27 to 92) during therapy, whereas no change was noted in the remaining four patients, none of whom had an objective response as compared with baseline. Among eight patients who had assessable results for paired biopsies and serial DCE-MRIs, there was no correlation between VEGFR levels or signaling response of VEGFR and pharmacokinetic parameters of DCE-MRI measurements.

CONCLUSION Sorafenib is relatively well-tolerated, with clinical and biologic antitumor activity in patients with metastatic papillary thyroid cancer, but it requires close surveillance and aggressive management of drug toxicity.

COMMENTARY

Studies of sorafenib have found the drug to have an impact on patients with metastatic tumor. Ratain et al. (1) found that patients with metastatic renal-cell carcinoma treated with sorafenib had median progression-free survival of 24 weeks as compared with 6 weeks for placebo (P = 0.007). Given the molecular pathophysiology of thyroid cancer and the spectrum of kinases inhibited by sorafenib, including Raf kinase, VEGFR, PDFR, and RET tyrosine kinases, Gupta-Abramson (2) conducted an open-label phase II trial to determine the efficacy of sorafenib in patients with advanced thyroid carcinoma. Patients with metastatic, iodine-refractory thyroid carcinoma received 400 mg of sorafenib orally twice daily. Thirty patients were entered into the study and treated for a minimum of 16 weeks. Seven patients (23%; 95% CI, 0.10 to 0.42) had a partial response lasting 18 to 84 weeks. Sixteen patients (53%; 95% CI, 0.34 to 0.72) had stable disease lasting 14 to 89 or more weeks. Seventeen (95%) of the 19 patients for whom serial thyroglobulin levels were available showed a rapid response in serum thyroglobulin levels, which decreased by a mean of 70%. Median progression-free survival was 79 weeks. Toxicity in this study was consistent with other sorafenib trials, although a single patient died of liver failure that was likely related to the treatment. The authors concluded that sorafenib has clinically relevant antitumor activity in patients with metastatic, radioiodine-refractory thyroid carcinoma, with an overall clinical benefit (partial response + stable disease) of 77%, a median progression-free survival of 79 weeks, and an overall acceptable safety profile. The authors opined that the results of this study represent a significant advance over chemotherapy in both response rate and progression-free survival, supporting further investigation of this drug in patients with thyroid cancer.

The Kloos et al. study is one of the first phase II clinical trials using an oral small-molecule multikinase inhibitor in patients with iodine-refractory metastatic PTC. The authors decided that sorafenib would be worthy of further study if the likelihood of a true response or target response rate was 30% or higher. The drug did not meet this expectation, and only 5 (15%) of 33 patients demonstrated a partial tumor response. Still, 23 patients had stable disease for longer than 6 months, and the median duration of the partial responses was 7.5 months, ranging from 6 to 14 months, and median progression-free survival was 15 months. Thyroglobulin declined more than 25% in 14 (78%) of 18 patients with PTC that had assessable thyroglobulin measurements.

Common grade 3 adverse events included hand–foot–skin reaction, musculoskeletal pain, fatigue, weight loss and diarrhea, and other adverse events. BRAF was detected in 17 (77%) of 22 PTCs analyzed. Four of 10 paired tumor biopsies

from patients with PTC showed a reduction in the levels of vascular VEGF phosphorylation, ERK phosphorylation, and VEGF expression during sorafenib therapy. No partial responses were found among patients with other forms of thyroid cancer. Stable disease and partial responses suggest a greater clinical benefit than that based on partial responses and stable disease of 6 months or more in 23 patients with PTC. Also, a better response is inferred from the serum Tg response.

Although the dose schedule used in this study was generally well tolerated, dose reductions were necessary in about half the patients. The authors suggest that the higher frequency of dose reductions in their study might be a result of relatively lower acceptability of long-term toxicities by patients with thyroid cancer. Still, the tumor response was generally maintained despite dose reductions.

Endocrinologists are not widely trained in the use of these drugs, but this study shows that the drug has benefits but also important complications. Physicians using these drugs must be aware of the adverse events of the drug and capable of quickly responding to this problem.

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References

1. Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2006;24:2505-12.

2. Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II trial of sorafenib in advanced thyroid cancer. J Clin Oncol 2008;26:4714-19.