ORIGINAL ARTICLE

Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

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ABSTRACT

BACKGROUND

Pazopanib and sunitinib provided a progression-free survival benefit, as compared with placebo or interferon, in previous phase 3 studies involving patients with metastatic renal-cell carcinoma. This phase 3, randomized trial compared the efficacy and safety of pazopanib and sunitinib as first-line therapy.

METHODS

We randomly assigned 1110 patients with clear-cell, metastatic renal-cell carcinoma, in a 1:1 ratio, to receive a continuous dose of pazopanib (800 mg once daily; 557 patients) or sunitinib in 6-week cycles (50 mg once daily for 4 weeks, followed by 2 weeks without treatment; 553 patients). The primary end point was progression-free survival as assessed by independent review, and the study was powered to show the noninferiority of pazopanib versus sunitinib. Secondary end points included overall survival, safety, and quality of life.

RESULTS

Pazopanib was noninferior to sunitinib with respect to progression-free survival (hazard ratio for progression of disease or death from any cause, 1.05; 95% confidence interval [CI], 0.90 to 1.22), meeting the predefined noninferiority margin (upper bound of the 95% confidence interval, <1.25). Overall survival was similar (hazard ratio for death with pazopanib, 0.91; 95% CI, 0.76 to 1.08). Patients treated with sunitinib, as compared with those treated with pazopanib, had a higher incidence of fatigue (63% vs. 55%), the hand–foot syndrome (50% vs. 29%), and thrombocytopenia (78% vs. 41%); patients treated with pazopanib had a higher incidence of increased levels of alanine aminotransferase (60%, vs. 43% with sunitinib). The mean change from baseline in 11 of 14 health-related quality-of-life domains, particularly those related to fatigue or soreness in the mouth, throat, hands, or feet, during the first 6 months of treatment favored pazopanib (P<0.05 for all 11 comparisons).

CONCLUSIONS

Pazopanib and sunitinib have similar efficacy, but the safety and quality-of-life profiles favor pazopanib. (Funded by GlaxoSmithKline Pharmaceuticals; COMPARZ ClinicalTrials.gov number, NCT00720941.)

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Renal-cell carcinoma is the most common kidney cancer.[1] Up to 30% of patients have metastases at the time of the initial diagnosis.[2] Systemic treatment for patients who have metastatic renal-cell carcinoma with a clear-cell histologic component has shifted from cytokines to drugs targeting angiogenesis. Sunitinib, pazopanib, and five other agents have been approved by the Food and Drug Administration for the treatment of clear-cell, metastatic renal-cell carcinoma.[3,4] Among the tyrosine kinase inhibitors, pazopanib and sunitinib are first-line treatment options.

Sunitinib has been compared with interferon alfa in patients who had not previously received systemic therapy for renal-cell carcinoma,[5] whereas pazopanib has been compared with placebo both in patients who had not received previous treatment and in those who had previously received cytokine therapy.[6] Comparison of efficacy across trials suggested similar progression-free survival benefits with pazopanib and sunitinib.[7] Comparison of safety suggested that pazopanib was associated with a lower incidence of fatigue, the hand–foot syndrome, stomatitis, and myelosuppression and with a higher incidence of liver-function abnormalities than was sunitinib.[7] The differences in the safety profile probably reflect differences in the selectivity of multitargeted kinases.[8] However, pazopanib and sunitinib have not been compared with each other in controlled studies.

In this phase 3, randomized trial, we compared the efficacy and safety of pazopanib and sunitinib in patients with metastatic renal-cell carcinoma as first-line treatment. The primary objective was to show noninferiority of pazopanib versus sunitinib with respect to progression-free survival.

Methods

Patients

Eligible patients were 18 years of age or older, had advanced or metastatic renal-cell carcinoma with a clear-cell histologic component, and had not received systemic treatment previously. Additional criteria were measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org),[9] a Karnofsky performance-status score of at least 70 (on a scale from 0 to 100, with 100 indicating normal functioning and lower scores indicating increasing disability) (Table S2 in the Supplementary Appendix),[10] and adequate organ function.

Exclusion criteria were brain metastases, poorly controlled hypertension, and cardiac and vascular conditions within 6 months before screening. All the patients provided written informed consent.

Study Design

The study was a randomized, open-label, phase 3 trial of pazopanib (Votrient, GlaxoSmithKline) versus sunitinib (Sutent, Pfizer). Randomization was stratified according to Karnofsky performance-status score (70 or 80 vs. 90 or 100), level of lactate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), and nephrectomy (yes vs. no). Patients were randomly assigned to one of the two study drugs in a 1:1 ratio in permuted blocks of four.

Pazopanib and sunitinib were provided by GlaxoSmithKline, the trial sponsor. Pazopanib was administered orally at a once-daily dose of 800 mg, with continuous dosing. Sunitinib was administered orally in 6-week cycles at a once-daily dose of 50 mg for 4 weeks, followed by 2 weeks without treatment. Dose reductions for pazopanib (to 600 mg and then to 400 mg) and sunitinib (to 37.5 mg and then to 25 mg) were determined according to the severity of adverse events. Patients were treated until progression of disease, the occurrence of unacceptable toxic effects, or withdrawal of consent.

The study was approved by the institutional review board or ethics committee at each participating center and was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. A data and safety monitoring board reviewed safety data during the study.

The academic authors and the sponsor developed the trial protocol together. All the authors had access to the primary data. Data were gathered by the investigators and analyzed by the sponsor. Final decisions regarding the content of the manuscript and the decision to submit the manuscript for publication were made by the academic principal investigator in consultation with other authors. The full study protocol is available at NEJM.org. All the authors vouch for the accuracy of the data reported and for adherence of the study to the protocol. The first draft of the manuscript was written by three of the academic authors and three authors who are em-

ployees of the sponsor. A medical writer paid by the sponsor assisted in manuscript preparation.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, defined as the period between the date of randomization and the date of the first documentation of disease progression or death from any cause. Secondary end points included the objective response rate, overall survival, safety, health-related quality of life, and medical resource utilization.

We performed disease assessments with the use of computed tomography or magnetic resonance imaging at baseline, every 6 weeks until week 24, and every 12 weeks thereafter until progression of disease. Imaging data were reevaluated by an independent review committee whose members were unaware of the treatment assignments to assess the primary end point and tumor response according to RECIST, version 1.0.[9] Patient follow-up continued until death or withdrawal from the study.

The duration of exposure for patients who discontinued treatment was defined as the period between the first and last doses of the drug and included interruptions, cycle delays, and the scheduled 2-week break from sunitinib. For both groups, laboratory tests were performed in 6-week cycles as follows: on days 1, 14, 28, and 42 of cycle 1; on days 28 and 42 of cycles 2 through 9; and on day 42 of subsequent cycles. Adverse events were graded according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 3.0.[11] Cardiac function was monitored on echocardiograms or multigated acquisition scans obtained every three cycles.

Health-related quality of life was assessed with the use of patient responses to the following instruments: Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F; on a scale from 0 to 52, with higher scores indicating less fatigue),[12] the 19-item Functional Assessment of Cancer Therapy (FACT) Kidney Symptom Index (FKSI-19; on a scale from 0 to 76, with higher scores indicating fewer symptoms),[13] Cancer Therapy Satisfaction Questionnaire (CTSQ; on a scale from 0 to 100, with higher scores indicating greater satisfaction),[14] and the Supplementary Quality of Life Questionnaire (SQLQ; on a scale from 0 to 3 for mouth, throat, hand, or foot soreness, with higher scores indicating more soreness or discomfort, and on a scale from 0 to 15 for limitations due to soreness, with higher scores indicating more limitations), which was adapted to the design of this trial. All the instruments were administered at baseline (except the CTSQ, which was relevant only after treatment), on day 28 of cycles 1 through 9, and on day 42 of subsequent cycles. After the protocol was amended to reduce the number of study visits by eliminating the day 28 visit, health-related quality-of-life assessments were obtained at day 42 of cycle 10 and subsequent cycles.

Variables related to health-related quality of life were assessed over the previous 7-day period for the FACIT-F and FKSI-19 questionnaires and over the previous 4-week period for the SQLQ and CTSQ. Primary end points regarding health-related quality of life were fatigue (as measured by the FACIT-F) and the treatment side-effects subscale of the FKSI-19 (three summed items regarding diarrhea, nausea, and general side effects). Secondary end points were the SQLQ, the CTSQ, and the other domains of the FKSI-19. At the visits scheduled for the health-related quality-of-life assessments, patients also reported medical resource utilization, including medical office visits that were not related to the study, telephone consultations, number of days in the hospital, and emergency department visits.

STATISTICAL ANALYSIS

We calculated that 631 disease-progression events were required for the study to have 80% power to reject the null hypothesis of an increased risk in the hazard of disease progression with pazopanib (hazard ratio, ≥1.25). The protocol was amended to increase the sample to 1100 patients after it became clear that the original planned enrollment of 876 patients would be insufficient to observe 631 independently reviewed disease-progression events. The target event count of 631 events did not change, so the power of the trial remained at 80%. Additional details are provided in the Methods section in the Supplementary Appendix.

Rather than reopen enrollment in the original trial, we achieved the targeted enrollment by amending the protocol to prospectively combine the sample in the original trial (927 patients) with the sample in the ongoing trial (ClinicalTrials.gov number, NCT01147822; 183 patients). The latter was a substudy of the original trial and was conducted in China, Taiwan, and South Korea (Fig.

S1 in the Supplementary Appendix). Because an analysis of pooled data from these trials was expected to be conducted for regional regulatory and reimbursement purposes, the trials were identical with regard to patient-selection criteria and design, except that health-related quality of life and medical resource utilization were not assessed in the substudy.

Efficacy data were analyzed in the intention-to-treat population (all patients who underwent randomization). Progression-free survival was shown to be noninferior if the upper bound of the 95% confidence interval for the hazard ratio, estimated with the use of a Cox proportional-hazards model adjusted for stratification factors, was less than 1.25 (noninferiority margin). The robustness of the primary analysis was tested with the use of prespecified sensitivity analyses, including analysis of data for the per-protocol population, Cox analysis without stratification for covariates, and analysis based on investigator review. The goal of these sensitivity analyses was consistency of the hazard-ratio estimates with the primary analysis. Cox analysis was used to analyze progression-free survival in patient subgroups defined according to baseline characteristics. No formal testing of the hypothesis was planned for any of the subgroup analyses, including the per-protocol analysis, given the issues of reduced sample size and multiple comparisons.

Overall survival was compared with the use of a stratified log-rank test. Objective response rates were compared with the use of Fisher's exact test. The relative risks of adverse events and the associated 95% confidence intervals (unadjusted for multiple comparisons) were estimated in the safety population (patients who received ≥1 dose of the study drug).

Changes in mean scores over time were analyzed for 11 of 14 health-related quality-of-life domains with the use of repeated-measures analysis of covariance (ANCOVA), with baseline score as the covariate. Three SQLQ measures regarding worst soreness were analyzed with the use of a Wilcoxon rank-sum test. The prespecified analysis was conducted during cycles 1 through 4 (up to 6 months), because issues regarding adverse events were expected to emerge during this period; however, in the ANCOVA, the covariance model was fit to cycles 1 through 8 (up to 12 months). The monthly rate of medical visits unrelated to the study, telephone consultations, number of days in the hospital, and emergency department visits through cycle 4 were compared across groups with the use of a Wilcoxon rank-sum test.

RESULTS

PATIENTS

From August 2008 through September 2011, a total of 1110 eligible patients were enrolled at sites in 14 countries in North America, Europe, Australia, and Asia. Demographic and clinical characteristics at baseline were balanced between the treatment groups (Table S3 in the Supplementary Appendix). A total of 8 patients (3 patients in the pazopanib group and 5 in the sunitinib group) did not receive any study therapy for various reasons, including withdrawal of consent. At the data-cutoff point in May 2012, a total of 486 of 554 patients (88%) in the pazopanib group and 483 of 548 (88%) in the sunitinib group had discontinued treatment (Fig. S2 in the Supplementary Appendix).

EFFICACY

Progression-free Survival

Disease-progression events occurred in 336 of 557 patients (60%) in the pazopanib group and in 323 of 553 (58%) in the sunitinib group. The median progression-free survival was 8.4 months with pazopanib (95% confidence interval [CI], 8.3 to 10.9) and 9.5 months with sunitinib (95% CI, 8.3 to 11.1). The point estimate of the hazard ratio for progression of disease or death from any cause with pazopanib versus sunitinib, according to independent review, was 1.05 (95% CI, 0.90 to 1.22), which met the predefined criterion for noninferiority (Fig. 1). The results of the progression-free survival analysis according to investigator review were similar (median progression-free survival, 10.5 months with pazopanib [95% CI, 8.3 to 11.1] and 10.2 months with sunitinib [95% CI, 8.3 to 11.1]; hazard ratio, 1.00; 95% CI, 0.86 to 1.15).

Analyses across predefined subgroups (Fig. S3 in the Supplementary Appendix) indicated that the results were not driven by any particular subgroup. Subgroup analyses showed similar results across ethnic groups, geographic regions, and the two trials (post hoc hazard ratio for progression of disease or death in the original study, 1.06; 95% CI, 0.90 to 1.24; hazard ratio in the substudy, 0.95; 95% CI, 0.60 to 1.48). With only 578 independently reviewed progression-free survival events,

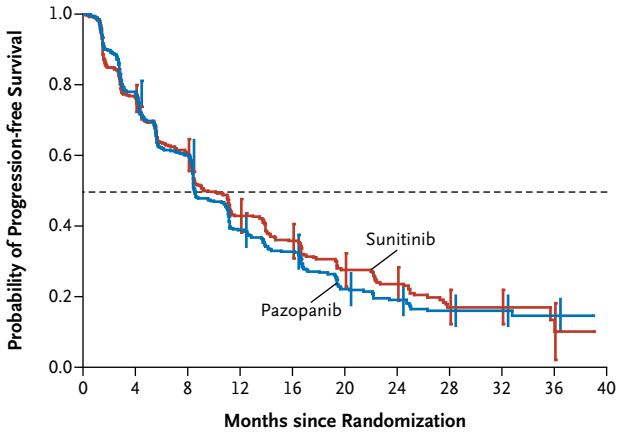

Figure 1. Kaplan–Meier Estimates of Progression-free Survival According to Independent Review.

The median progression-free survival was 8.4 months with pazopanib (95% CI, 8.3 to 10.9) and 9.5 months with sunitinib (95% CI, 8.3 to 11.1). The dotted line represents the median (0.5), and vertical lines represent 95% confidence intervals.

the subgroup analysis from the original study still met the noninferiority criterion. The results of the progression-free survival analysis in the per-protocol population were consistent with the results of the primary analysis (hazard ratio for progression of disease or death, 1.07; 95% CI, 0.91 to 1.25).

Tumor Response and Overall Survival

According to independent review, partial responses were observed in 170 patients in the pazopanib group (31%) and in 134 in the sunitinib group (24%). Complete responses were observed in 1 patient in the pazopanib group and in 3 in the sunitinib group. Objective response rates were higher with pazopanib than with sunitinib (31% vs. 25%, P=0.03). Investigator-assessed objective response rates were similar between the two groups (33% in the pazopanib group and 29% in the sunitinib group, P=0.12) (Table S4 in the Supplementary Appendix).

A total of 502 deaths occurred. The median overall survival was 28.4 months in the pazopanib group (95% CI, 26.2 to 35.6) and 29.3 months in the sunitinib group (95% CI, 25.3 to 32.5). Overall survival was similar in the two groups (hazard ratio for death with pazopanib vs. sunitinib, 0.91; 95% CI, 0.76 to 1.08; P=0.28 by a stratified log-rank test) (Fig. S4 in the Supplementary Appendix).

SAFETY

The median duration of treatment was similar in the two groups: 8.0 months (range, 0 to 40) in the pazopanib group and 7.6 months (range, 0 to 38) in the sunitinib group. Similar percentages of patients in the pazopanib and sunitinib groups had a dose interruption of 7 days or more (44% and 49%, respectively) or a reduction in the dose (44% and 51%, respectively). The proportion of patients who discontinued the study drug because of adverse events was 24% in the pazopanib group and 20% in the sunitinib group (Table S5 in the Supplementary Appendix); the higher discontinuation rate observed for pazopanib, as compared with sunitinib, was primarily due to abnormalities in liver-function tests (6% vs. 1%).

The most common adverse events included diarrhea, fatigue, hypertension, and nausea (Table S6 in the Supplementary Appendix). Common adverse events of any grade (occurring in >10% of patients in either group) that were reported more frequently with sunitinib than with pazopanib and for which the difference in frequency was significant included the hand–foot syndrome, mucosal inflammation, stomatitis, hypothyroidism, dysgeusia, dyspepsia, epistaxis, and fatigue (Table 1). By contrast, the adverse events of any grade that were reported significantly more frequently with pazopanib than with sunitinib were changes in hair color, weight loss, and alopecia. Patients in the sunitinib group had a higher incidence of grade 3 or 4 fatigue and the hand–foot syndrome than did those in the pazopanib group.

Patients in the sunitinib group had a higher risk of hematologic laboratory abnormalities of any grade and of grades 3 and 4, including leukopenia, thrombocytopenia, neutropenia, and anemia, than did those in the pazopanib group. By contrast, patients who received pazopanib had a higher risk of increased levels of alanine aminotransferase or bilirubin of any grade and a higher risk of increased levels of alanine aminotransferase or aspartate aminotransferase of grade 3 or 4.

There were no between-group differences in the rates of cardiovascular adverse events. The percentages of patients meeting cardiac-dysfunction criteria[15] were similar: 13% in the pazopanib group and 11% in the sunitinib group (Table S7 in the Supplementary Appendix). The incidence of myocardial infarction or ischemia was similar in the pazopanib and sunitinib groups (2% and 4%, respectively).

Table 1. Adverse Events and Laboratory Abnormalities during Treatment for Which the Relative Risk Differed Significantly between Groups.*

Event	Pazopanib (N=554)			Sunitinib (N=548)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Adverse events						
Increased risk with sunitinib — no. of patients (%)†						
Fatigue‡	302 (55)	58 (10)	1 (<1)	344 (63)	92 (17)	2 (<1)
Hand–foot syndrome‡	163 (29)	32 (6)	0	275 (50)	62 (11)	2 (<1)
Dysgeusia	143 (26)	1 (<1)	0	198 (36)	0	0
Rash	97 (18)	4 (1)	0	125 (23)	4 (1)	0
Constipation	94 (17)	4 (1)	0	130 (24)	5 (1)	0
Dyspepsia	78 (14)	0	0	133 (24)	3 (1)	0
Stomatitis	77 (14)	4 (1)	0	150 (27)	8 (1)	0
Hypothyroidism	67 (12)	0	0	133 (24)	2 (<1)	0
Pain in a limb	67 (12)	2 (<1)	0	91 (17)	6 (1)	0
Mucosal inflammation‡	61 (11)	3 (1)	0	141 (26)	16 (3)	0
Peripheral edema	59 (11)	1 (<1)	0	91 (17)	2 (<1)	0
Epistaxis	48 (9)	1 (<1)	0	97 (18)	6 (1)	0
Pyrexia	48 (9)	2 (<1)	0	88 (16)	6 (1)	0
Increased blood LDH	39 (7)	2 (<1)	0	58 (11)	3 (1)	0
Increased blood thyrotropin	31 (6)	0	0	66 (12)	0	0
Gastroesophageal reflux disease	19 (3)	1 (<1)	0	56 (10)	2 (<1)	0
Yellow skin	4 (1)	0	0	83 (15)	0	0
Increased risk with pazopanib — no. of patients (%)§						
Changes in hair color	168 (30)	0	0	53 (10)	1 (<1)	0
Weight loss	84 (15)	5 (1)	0	33 (6)	1 (<1)	0
Alopecia	75 (14)	0	0	45 (8)	0	0
Hematologic and other laboratory abnormalities						
Increased risk with sunitinib — no. of patients/total no. (%)¶						
Leukopenia‡	237/548 (43)	8/548 (1)	0/548	423/542 (78)	34/542 (6)	0/542
Thrombocytopenia‡	227/548 (41)	17/548 (3)	3/548 (1)	421/542 (78)	95/542 (18)	22/542 (4)
Lymphocytopenia‡	208/548 (38)	29/548 (5)	0/548	300/542 (55)	76/542 (14)	1/542 (<1)
Neutropenia‡	203/548 (37)	20/548 (4)	5/548 (1)	370/542 (68)	103/542 (19)	6/542 (1)
Anemia‡	171/548 (31)	7/548 (1)	5/548 (1)	326/542 (60)	34/542 (6)	6/542 (1)
Hypophosphatemia‡	193/539 (36)	24/539 (4)	0/539	279/533 (52)	44/533 (8)	5/533 (1)
Hypoalbuminemia	179/544 (33)	4/544 (1)	0/544	225/539 (42)	9/539 (2)	0/539
Increased creatinine	177/548 (32)	4/548 (1)	0/548	250/542 (46)	5/542 (1)	3/542 (1)
Hypomagnesemia‡	125/539 (23)	1/539 (<1)	0/539	128/535 (24)	6/535 (1)	1/535 (<1)
Hypermagnesemia‡	62/539 (12)	13/539 (2)	0/539	97/535 (18)	25/535 (5)	0/535
Increased risk with pazopanib — no. of patients/total no. (%)						
Increased AST‖	333/547 (61)	62/547 (11)	7/547 (1)	323/541 (60)	15/541 (3)	0/541
Increased ALT§‖	326/547 (60)	84/547 (15)	12/547 (2)	234/540 (43)	19/540 (4)	2/540 (<1)
Increased total bilirubin§	199/546 (36)	16/546 (3)	2/546 (<1)	144/541 (27)	11/541 (2)	2/541 (<1)
Increased alkaline phosphatase‖	154/547 (28)	17/547 (3)	0/547	131/540 (24)	5/540 (1)	0/540
Hypoglycemia§	83/548 (15)	2/548 (<1)	0/548	57/541 (11)	3/541 (1)	0/541

* Events listed are those that occurred in more than 10% of patients. A difference in relative risk was considered to be significant when the 95% confidence interval for relative risk did not include unity. These confidence intervals were not corrected for multiple comparisons. Increased levels of blood lactate dehydrogenase (LDH) and blood thyrotropin are not graded according to the Common Terminology Criteria for Adverse Events and were reported as adverse events when the investigator considered them clinically significant. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

† The relative risk of an event of any grade was significantly higher with sunitinib than with pazopanib.

‡ The relative risk of a grade 3 or 4 event was significantly higher with sunitinib than with pazopanib.

§ The relative risk of an event of any grade was significantly higher with pazopanib than with sunitinib.

¶ Except for hypomagnesemia, the relative risk of an event of any grade was significantly higher with sunitinib than with pazopanib.

‖ The relative risk of a grade 3 or 4 event was significantly higher with pazopanib than with sunitinib.

Fatal adverse events were reported for 13 patients in the pazopanib group (2%) and for 19 in the sunitinib group (3%). Drug-related fatal adverse events occurred in 3 patients in the pazopanib group (1%) and in 8 in the sunitinib group (1%).

Because the dosing schedules for pazopanib (continuous) and sunitinib (intermittent) differ, patterns of hematologic laboratory abnormalities on day 28 versus day 42 during the first eight cycles of therapy were examined. The incidence of hematologic laboratory abnormalities among patients in the pazopanib group was relatively constant and generally lower, over the entire study period, than the incidence among patients in the sunitinib group (Fig. S5 and S6 in the Supplementary Appendix). The incidence and severity of thrombocytopenia and neutropenia among patients in the sunitinib group peaked at day 28 of each cycle and were reduced at day 42, although not to baseline levels. In contrast, the incidence and severity of anemia peaked at day 42, as compared with day 28, the last day of active sunitinib dosing. These data are consistent with the higher mean hemoglobin levels in the pazopanib group than in the sunitinib group, at day 28 (mean values for cycles 1 through 8 ranged from 13.8 to 14.1 g per deciliter for pazopanib vs. 13.2 to 13.5 g per deciliter for sunitinib) and at day 42 (mean values for cycles 1 through 8 ranged from 13.7 to 14.1 g per deciliter for pazopanib vs. 11.8 to 12.2 g per deciliter for sunitinib).

HEALTH-RELATED QUALITY OF LIFE

During the first 6 months of treatment, the health-related quality-of-life scores in the pazopanib group were better than those in the sunitinib group for both primary end points (fatigue and treatment side effects) (Table 2). Significant differences favored pazopanib over sunitinib for 11 of 14 comparisons regarding health-related quality of life. Seven of these differences had effect sizes of a magnitude conventionally viewed as small to medium (i.e., range, 0.20 to 0.50)[16,17]; the difference in mouth and throat soreness was larger, in the medium-to-large range for effect size (i.e., 0.50 to 0.80); all other significant differences had effect sizes of less than 0.20 (Table 2).

Patients had significantly less fatigue and foot soreness with pazopanib than with sunitinib (Fig. 2). After the protocol amendment to reduce the number of study visits by eliminating the day 28 visit, health-related quality-of-life assessments were obtained at day 42 of cycle 10 and subsequent cycles. Numerical differences with respect to fatigue and foot soreness between the two treatment groups followed a similar pattern; however, these data were limited by the small numbers of patients (Fig. S7 in the Supplementary Appendix).

MEDICAL RESOURCE UTILIZATION

As compared with patients who received sunitinib, patients who received pazopanib had fewer monthly telephone consultations ($P=0.04$) and emergency department visits ($P=0.003$). Although the numbers of medical visits unrelated to the study and hospital days per month were numerically lower in the pazopanib group, the differences were not significant (Table S8 in the Supplementary Appendix).

DISCUSSION

With multiple, approved treatment options available for metastatic renal-cell cancer, head-to-head comparisons are needed to inform the choice of treatment. This phase 3, randomized study showed noninferiority of progression-free survival with pazopanib versus sunitinib. The similar rates of overall survival in the two groups and the higher objective response rates observed with pazopanib versus sunitinib are consistent with noninferiority in overall efficacy.

When agents with similar efficacy are options for first-line therapy, the safety profile assumes greater importance in determining treatment choice.[18,19] In this study, the pazopanib and sunitinib groups had similar rates of dose reduction and drug discontinuation because of adverse events. However, the safety profiles of the two drugs differed. Elevations in liver-function tests, weight loss, and changes in hair color were more common with pazopanib than with sunitinib. Most adverse events, particularly those associated with discomfort, such as fatigue, the hand–foot syndrome, and mouth sores, occurred more frequently with sunitinib than with pazopanib. Fatigue, gastrointestinal events, the hand–foot syndrome, mouth sores, and liver toxicity have been highlighted as adverse events of particular concern to patients.[18,19]

Our analyses of health-related quality of life showed that patients who received pazopanib reported less fatigue, fewer side effects such as soreness of the hand or foot and soreness of the mouth or throat, and better satisfaction with treatment than did those who received sunitinib,

Table 2. Change in Health-Related Quality of Life during the First 6 Months for 927 Patients Treated in the Study.*

Instrument	Pazopanib	Sunitinib	Pooled Standard Deviation†	Difference in Mean Change from Baseline Score with Pazopanib vs. Sunitinib‡	P Value§	Drug Favored According to Significant Difference¶	Effect Size‖
	number of patients						
FACIT-F**	377	403	9.64	2.32	<0.001	Pazopanib	0.24
FKSI-19							
Treatment side effects**	351	382	2.28	0.31	0.03	Pazopanib	0.14
Disease-related physical symptoms	378	407	5.97	0.78	0.03	Pazopanib	0.13
Disease-related emotional symptoms	370	402	1.19	–0.05	0.41	Neither	–0.04
Functional well-being	378	403	3.56	0.31	0.10	Neither	0.09
Total score	377	408	9.79	1.41	0.02	Pazopanib	0.14
CTSQ							
Expectations of therapy	414	421	19.25	1.41	0.28	Neither	0.07
Feelings about side effects	401	413	20.92	8.50	<0.001	Pazopanib	0.41
Satisfaction with therapy	408	417	13.95	3.21	<0.001	Pazopanib	0.23
SQLQ							
Worst mouth or throat soreness	215	194	0.76	–0.51	<0.001	Pazopanib	–0.67
Worst hand soreness	219	195	0.63	–0.20	0.002	Pazopanib	–0.32
Worst foot soreness	217	195	0.81	–0.27	0.001	Pazopanib	–0.33
Limitations due to mouth or throat soreness	196	185	2.11	0.94	<0.001	Pazopanib	0.45
Limitations due to foot soreness	190	180	2.78	0.65	0.01	Pazopanib	0.23

* Scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) range from 0 to 52, with higher scores indicating less fatigue. Scores on the 19-item Functional Assessment of Cancer Therapy (FACT) Kidney Symptom Index (FKSI-19) range from 0 to 76, with higher scores indicating fewer symptoms. Scores on the Cancer Therapy Satisfaction Questionnaire (CTSQ) range from 0 to 100, with higher scores indicating greater satisfaction. Scores on the Supplementary Quality of Life Questionnaire (SQLQ) range from 0 to 3 for mouth, hand, or foot soreness, with higher scores indicating more soreness or discomfort, and from 0 to 15 for limitations due to soreness, with higher scores indicating more limitations. Data were included for patients for whom at least one score was available in cycles 1 through 4. Patients with missing baseline scores were excluded from the analyses. Many patients did not have SQLQ scores at baseline because this questionnaire was included in the study as part of a protocol amendment. This also affected the rate of compliance in completing the SQLQ (85%) because there was uncertainty at some study sites regarding when to introduce the questionnaire. Overall compliance for the entire sample of all the other questionnaires across cycles 1 through 4 was 93%, with no differences between treatment groups.

† The pooled standard deviation was calculated either for the average change from baseline at cycles 1 through 4, for the FACIT-F, FKSI, and SQLQ scores, or for the average of the scores at cycles 1 through 4, for the CTSQ.

‡ The mean change was derived from the prespecified analysis of covariance (ANCOVA) for all measures except the worst-soreness measures of the SQLQ. For those measures, the mean change reflects the average of the change from baseline to the average scores from cycles 1 through 4.

§ The P value was calculated with the use of the prespecified ANCOVA analysis for all measures except the worst-soreness measures of the SQLQ, for which the P value was calculated with the use of a Wilcoxon rank-sum test.

¶ Significant differences were those with a P value of less than 0.05.

‖ The effect size was the size of the difference between the two treatments and was calculated by dividing the difference in the mean change by the pooled standard deviation. Regardless of direction, the absolute value of an effect size was defined as follows: 0.20 was small, 0.50 medium, and 0.80 large.[16,17] By convention,[16] any difference in an effect size of less than 0.20 was considered unlikely to be important.

** This end point was a prespecified primary health-related quality-of-life end point.

findings that are consistent with the safety results. The timing of the assessment on day 28 was intended to capture health-related quality of life while patients were actively taking the study drug. The assessment on day 28, as opposed to the assessment on day 42 or the combined assessments on days 28 and 42, could be interpreted as biased toward pazopanib because it may not

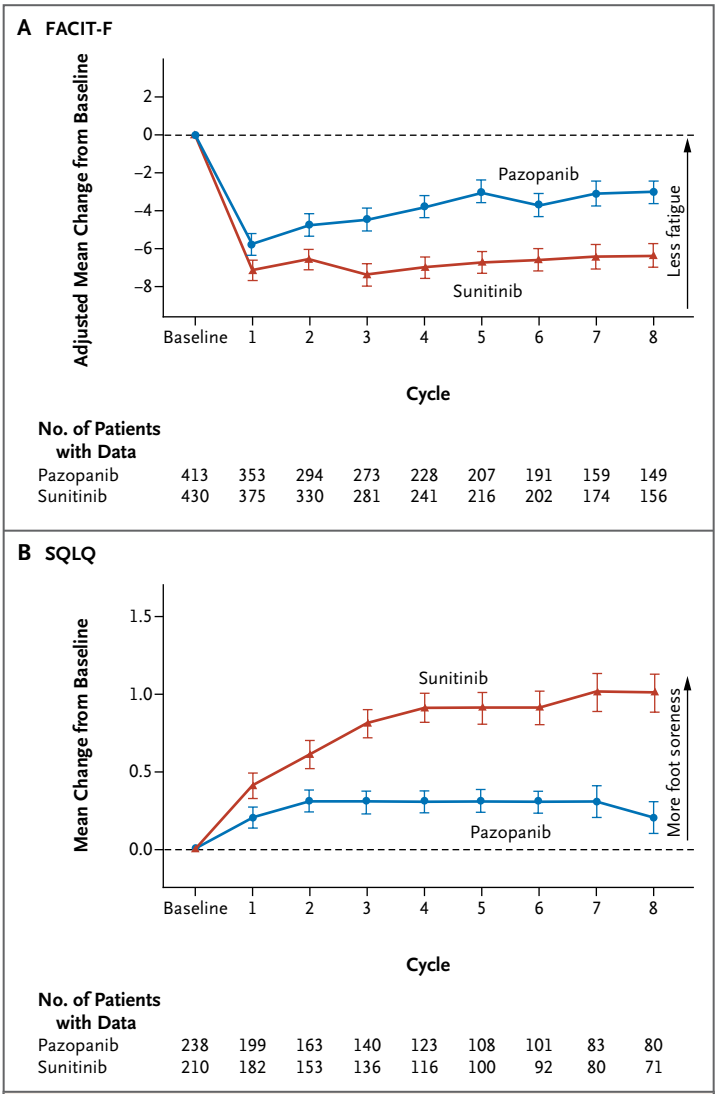

Figure 2. Adjusted Mean Change from Baseline in Fatigue Score and Mean Change from Baseline in Worst Foot Soreness.

Panel A shows the adjusted mean change from baseline in the fatigue score on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) questionnaire.[12] Scoring is based on a scale from 0 to 52, with higher scores indicating less fatigue. The adjusted mean changes were obtained from an analysis of covariance adjusted for baseline score with the use of mixed-model repeated measures. Panel B shows the mean change from baseline in the score for worst foot soreness on the Supplementary Quality of Life Questionnaire (SQLQ). Scoring is based on a scale from 0 to 3 for foot soreness, with higher scores indicating more soreness or discomfort. The assessments were conducted on day 28 of each numbered cycle. The dashed line in each graph represents no change from baseline, and I bars represent 1 SE.

have captured the recovery of patients in the sunitinib group during the 2-week drug holiday. One randomized, phase 2 trial evaluated the efficacy and safety of sunitinib for intermittent versus continuous dosing.[20] Although no significant difference in safety or overall health-related quality of life between these sunitinib schedules was observed, patient fatigue fluctuated more with the intermittent schedule, with worse scores at day 28 than at day 42.

To assess this point in our study, hematologic adverse events were compared at day 28 and day 42. Although recovery from sunitinib toxicity was observed with respect to thrombocytopenia and neutropenia, anemia was more severe at day 42 than at day 28. Previous cross-sectional and longitudinal studies have shown a significant correlation between anemia and fatigue in patients with cancer, such that lower hemoglobin levels are associated with worse fatigue.[12,21] To the extent that group differences in fatigue were driven by anemia, the health-related quality-of-life assessment on day 28, versus the assessment on day 42, represents a conservative estimate of the fatigue-reducing benefit with pazopanib.

Our findings are supported by the results of a second study, presented at two oncology meetings in 2012, which compared health-related quality of life (but not efficacy) with pazopanib versus sunitinib.[22,23] In that blinded study, patients were randomly assigned to receive sequential treatment with sunitinib followed by pazopanib, or vice versa, over a 22-week period, and the FACIT-F and SQLQ instruments were administered every 2 weeks (on days 14, 28, and 42).[22,23] Analyses of the responses to these questionnaires showed that the patients treated with pazopanib reported having less fatigue, soreness of the hand or foot, and soreness of the mouth or throat than did the patients treated with sunitinib.[22,23]

The management of adverse events resulting from the use of targeted agents is known to increase medical treatment costs and medical resource utilization.[24] Our study showed lower monthly use of medical resources with pazopanib than with sunitinib. These end points, plus health-related quality of life and the safety profile, assume special importance in comparative-effectiveness research when clinically similar (noninferior) treatments are being considered.

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APPENDIX

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