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Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

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ABSTRACT

BACKGROUND

The multitargeted tyrosine kinase inhibitor sunitinib has shown activity against pancreatic neuroendocrine tumors in preclinical models and phase 1 and 2 trials.

METHODS

We conducted a multinational, randomized, double-blind, placebo-controlled phase 3 trial of sunitinib in patients with advanced, well-differentiated pancreatic neuroendocrine tumors. All patients had Response Evaluation Criteria in Solid Tumors–defined disease progression documented within 12 months before baseline. A total of 171 patients were randomly assigned (in a 1:1 ratio) to receive best supportive care with either sunitinib at a dose of 37.5 mg per day or placebo. The primary end point was progression-free survival; secondary end points included the objective response rate, overall survival, and safety.

RESULTS

The study was discontinued early, after the independent data and safety monitoring committee observed more serious adverse events and deaths in the placebo group as well as a difference in progression-free survival favoring sunitinib. Median progression-free survival was 11.4 months in the sunitinib group as compared with 5.5 months in the placebo group (hazard ratio for progression or death, 0.42; 95% confidence interval [CI], 0.26 to 0.66; P<0.001). A Cox proportional-hazards analysis of progression-free survival according to baseline characteristics favored sunitinib in all subgroups studied. The objective response rate was 9.3% in the sunitinib group versus 0% in the placebo group. At the data cutoff point, 9 deaths were reported in the sunitinib group (10%) versus 21 deaths in the placebo group (25%) (hazard ratio for death, 0.41; 95% CI, 0.19 to 0.89; P=0.02). The most frequent adverse events in the sunitinib group were diarrhea, nausea, vomiting, asthenia, and fatigue.

CONCLUSIONS

Continuous daily administration of sunitinib at a dose of 37.5 mg improved progression-free survival, overall survival, and the objective response rate as compared with placebo among patients with advanced pancreatic neuroendocrine tumors. (Funded by Pfizer; ClinicalTrials.gov number, NCT00428597.)

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Pancreatic neuroendocrine tumors are uncommon tumors arising from endocrine cells of the pancreas.[1] Surgery is the mainstay of treatment for resectable disease,[2] and therapy directed to the liver may have some palliative benefit for metastases that occur predominantly in the liver.[3,4] Somatostatin analogues relieve symptoms resulting from hormone hypersecretion in functioning tumors and may delay disease progression in selected patients.[5-7] Streptozocin alone or in combination with doxorubicin remains the only chemotherapeutic agent approved for the treatment of advanced pancreatic neuroendocrine tumors,[8-11] though the magnitude of benefit has been challenged.[12,13]

Vascular endothelial growth factor (VEGF) is a key driver of angiogenesis in pancreatic neuroendocrine tumors.[14,15] Tissue from malignant pancreatic endocrine tumors also shows widespread expression of platelet-derived growth factor receptors (PDGFRs) α and β, stem-cell factor receptor (c-kit), and VEGF receptor (VEGFR)-2 and VEGFR-3.[16-18] Sunitinib malate (Sutent, Pfizer) inhibits these kinases[19,20] and delays tumor growth in a RIP1-Tag2 transgenic mouse model of pancreatic islet-cell tumors by reducing endothelial-cell density and pericyte coverage of tumor vessels.[21,22] In phase 1 and 2 trials, sunitinib showed antitumor activity in patients with pancreatic neuroendocrine tumors.[23,24] On the basis of these findings, we conducted a phase 3, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of continuous daily administration of sunitinib at a dose of 37.5 mg per day in patients with advanced pancreatic neuroendocrine tumors.

METHODS

PATIENTS

Eligible patients had pathologically confirmed, well-differentiated pancreatic endocrine tumors that were advanced, metastatic, or both,[25,26] and they were not candidates for surgery. Additional inclusion criteria were the following: documented disease progression within the previous 12 months as assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST[27]); one or more measurable target lesions; an Eastern Cooperative Oncology Group performance status of 0 or 1 (with 0 indicating that the patient is fully active and 1 that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature [e.g., light housework or office work]); and adequate hematologic, hepatic, and renal function. The Ki-67 index (the percentage of cells that were positive for Ki-67, determined by immunostaining of the primary tumor) was assessed at screening from available pathology reports. Patients with poorly differentiated pancreatic neuroendocrine tumors,[25] previous tyrosine kinase or VEGF inhibitor treatment, cardiac events or pulmonary embolism in the previous 12 months, ongoing cardiac dysrhythmias or a prolonged QT interval corrected for heart rate (QTc), symptomatic brain metastases, or a left ventricular ejection fraction of 50% or less were excluded.

The trial was approved by the institutional review board or ethics committee at each center and complied with Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. All patients provided written informed consent.

TRIAL DESIGN

This multinational, randomized, double-blind, placebo-controlled, phase 3 trial was funded by Pfizer. Patients were randomly assigned in a 1:1 ratio to receive once-daily oral sunitinib at a dose of 37.5 mg per day or matching placebo. In patients with other types of tumors, continuous administration of sunitinib at a dose of 37.5 mg per day is similar to intermittent administration with respect to the predicted blood level, safety profile, and time to tumor progression.[28,29]

Treatment interruptions and a dose reduction to 25 mg per day were permitted to manage adverse events, with a subsequent increase in dose if toxicity of grade 2 or higher did not recur. In patients without an objective tumor response who had grade 1 or lower nonhematologic or grade 2 or lower hematologic treatment-related adverse events during the first 8 weeks, the dose could be increased to 50 mg per day. Treatment continued until RECIST-defined progression was documented, unacceptable adverse events occurred, or the patient died. Patients with disease progression while receiving placebo could enter an open-label sunitinib extension protocol (A Treatment Protocol for Patients Continuing from Prior SU11248 Protocol, ClinicalTrials.gov number, NCT00443534, or A Continuation Study Using Sunitinib Malate for Patients Leaving Treatment on a Previous Sunitinib Study, NCT00428220). Before the trial, during the trial, or both, patients could receive somatostatin analogues at the investigator's discretion.

The trial was designed by Pfizer in conjunction with the investigators. Data collection and statistical analyses were performed by the sponsor. The initial draft of the manuscript was prepared by the first author in collaboration with the sponsor and professional medical writers paid by the sponsor. All authors had access to the data and contributed to subsequent drafts. The conduct of the trial was overseen by an independent data and safety monitoring committee that had access to safety and efficacy data. The academic authors vouch for the completeness and accuracy of the data, the data analyses, and the fidelity of this report to the study protocol (available with the full text of this article at NEJM.org).

ASSESSMENTS AND OUTCOMES

Data and patient-reported outcomes were recorded every 4 weeks (one cycle) during clinic visits. Clinical assessments, biologic measurements, and full tumor imaging were performed at screening; subsequent imaging was performed during week 5 and week 9 and every 8 weeks thereafter, whenever progression was suspected, and at the end of treatment or withdrawal from the study. Compliance and safety were assessed every 4 weeks and at the end of treatment.

The primary end point was progression-free survival, defined as the time from randomization to the first evidence of progression or death from any cause. For patients with inadequate baseline assessments, data on the progression-free survival time were censored on the date of randomization, with a 1-day duration.

Secondary efficacy end points included overall survival, the objective response rate, the time to tumor response, the duration of response, safety, and patient-reported outcomes. Tumor response was assessed by investigators with the use of RECIST. Confirmed responses were those that persisted on repeat imaging 4 weeks or more after initial documentation. Safety assessments included documentation of adverse events with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf), hematologic and biochemical laboratory tests, physical examination, and vital-sign measurements. The self-administered European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30, version 3.0) was used to measure patient-reported outcomes.[30]

STATISTICAL ANALYSIS

Efficacy was assessed in the intention-to-treat population on the basis of investigator-assessed tumor response. Kaplan-Meier methods were used to obtain estimates of median progression-free survival, with corresponding two-sided 95% confidence intervals. The Cox proportional-hazards model was used to calculate hazard ratios. A target sample of 340 patients was estimated on the basis of a total of 260 events required for 90% power to detect a 50% increase in progression-free survival with sunitinib from an estimated median progression-free survival of 5.1 months with placebo, with the use of a two-sided, unstratified log-rank test adjusted for one interim analysis after the first 130 events. The nominal significance level for the interim and final progression-free survival analyses was determined by means of the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary, with an overall two-sided type I error rate of 5%. Exploratory regression analyses with the use of the Cox proportional-hazards model were performed to test the influence of baseline characteristics on progression-free survival. Fisher's exact test was used to compare the objective response rate between study groups. Overall survival was analyzed with the use of Kaplan-Meier methods. The duration of response and time to tumor response were analyzed with the use of descriptive statistics.

The QLQ-C30 questionnaire was scored with the use of the QLQ-C30 scoring manual[31] and interpreted with the use of a minimally-important-difference approach.[32] Patient-reported outcomes were analyzed with the use of a repeated-measures, mixed-effects model (which included all 15 QLQ-C30 scales and items). Safety was assessed in patients who received one or more doses of a study drug.

RESULTS

PATIENTS

Between June 2007 and April 2009, a total of 171 patients were randomly assigned to a study group. In February 2009, the data and safety monitoring committee convened for ongoing safety monitoring and assessed data on 154 patients who had undergone randomization up to that point. The committee recommended discontinuation of the trial because of the greater number of deaths and serious adverse events in the placebo group and the difference in progression-free survival favor-

ing sunitinib; as a result of this recommendation, the trial was closed. The last patient received a study drug in April 2009; study-group assignments were revealed at that time, and patients were offered open-label sunitinib treatment in a separate trial (NCT00443534 or NCT00428220). A total of 44 patients in the sunitinib group and 59 patients in the placebo group entered these studies. Because of the early trial closure, 3 patients in the sunitinib group and 2 patients in the placebo group did not receive the study drug; in addition, 1 patient in the placebo group had a protocol violation and did not receive placebo (see Fig. 1 in the Supplementary Appendix, available at NEJM.org).

Patients were enrolled at 42 centers in 11 countries. Baseline characteristics were similar between the two study groups (Table 1).

Table 1. Demographic and Baseline Characteristics of the Patients.

Variable	Sunitinib (N=86)	Placebo (N=85)
Age		
Median — yr	56	57
Range — yr	25–84	26–78
≥65 yr — no. (%)	22 (26)	23 (27)
Sex — no. (%)		
Male	42 (49)	40 (47)
Female	44 (51)	45 (53)
Race — no. (%)*		
White	48 (56)	53 (62)
Asian	13 (15)	10 (12)
Other or unspecified†	25 (29)	22 (26)
Geographic region — no. (%)		
Europe	59 (69)	56 (66)
Asia	11 (13)	10 (12)
Americas or Australia	16 (19)	19 (22)
ECOG performance status — no. (%)‡§		
0	53 (62)	41 (48)
1	33 (38)	43 (51)
2	0	1 (1)¶
Inherited genetic conditions — no. (%)		
Multiple endocrine neoplasia type 1	0	2 (2)
Von Hippel–Lindau disease	2 (2)	0
Time since diagnosis — yr‖		
Median	2.4	3.2
Range	0.1–25.6	0.1–21.3
Tumor functionality — no. (%)§**		
Nonfunctioning	42 (49)	44 (52)
Functioning		
Gastrinoma	9 (10)	10 (12)
Glucagonoma	3 (3)	2 (2)
Insulinoma	2 (2)	2 (2)
Vasoactive intestinal peptide–secreting tumor	0	2 (2)
Somatostatinoma	1 (1)	0
Other, multisecretory, or unknown	10 (12)	5 (6)
Not specified	19 (22)	20 (24)

Table 1. (Continued.)

Variable	Sunitinib (N=86)	Placebo (N=85)
Ki-67 index		
No. of patients with data that could be evaluated	36	36
Index — no. (%)		
≤2%	7 (19)	6 (17)
>2%–5%	16 (44)	14 (39)
>5%–10%	5 (14)	10 (28)
>10%	8 (22)	6 (17)
No. of sites of disease — no. (%)§		
1	30 (35)	23 (27)
2	31 (36)	26 (31)
≥3	24 (28)	35 (41)
Not reported	1 (1)	1 (1)
Presence of distant metastases — no. (%)		
Any, including hepatic	82 (95)	80 (94)
Extrahepatic	21 (24)	34 (40)
Previous treatment — no. (%)§		
Surgery	76 (88)	77 (91)
Radiation therapy	9 (10)	12 (14)
Chemoembolization	7 (8)	14 (16)
Radiofrequency ablation	3 (3)	6 (7)
Percutaneous ethanol injection	1 (1)	2 (2)
Somatostatin analogues††	30 (35)	32 (38)
Previous systemic chemotherapy — no. (%)		
Any	57 (66)	61 (72)
Streptozocin	24 (28)	28 (33)
Anthracyclines	27 (31)	35 (41)
Fluoropyrimidines	20 (23)	25 (29)

* Race was self-reported.
† In accordance with local regulations, data on race were not routinely collected in one participating country.
‡ The Eastern Cooperative Oncology Group (ECOG) performance status is based on an assessment of activities of daily living, on a scale from 0 (fully active) to 5 (dead).
§ The study groups did not differ significantly (P>0.05 by Fisher's exact test) with respect to ECOG performance status (0 vs. 1 or 2), tumor functional status (nonfunctioning vs. other), the number of involved disease sites (<3 vs. ≥3), and the number of previous systemic regimens (<2 vs. ≥2).
¶ Enrollment of this patient was a protocol deviation.
‖ Data were available for 85 patients in each group.
** Tumor functionality was reported by investigators. On the basis of the investigators' assessment, patients included in the "unknown" category had clinical symptoms but no identified corresponding neuropeptide secretion.
†† This category includes patients who received somatostatin analogues (predominantly octreotide, octreotide acetate, and lanreotide) before the first dose of study drug, regardless of whether they continued receiving somatostatin analogues concomitantly with the study drug.

STUDY TREATMENT

Patients received sunitinib for a median duration of 4.6 months (range, 0.4 to 17.5), and patients received placebo for a median duration of 3.7 months (range, 0.03 to 20.2). Nineteen patients (22%) who were randomly assigned to sunitinib remained in the study for more than 1 year, as compared with four patients who were randomly assigned to placebo (5%).

The most common reasons for study discon-

tinuation were disease progression (in 19 patients who received sunitinib [22%] and in 47 patients who received placebo [55%]), termination of the trial (in 41 patients who received sunitinib [48%] and in 16 patients who received placebo [19%]), and adverse events (in 15 patients who received sunitinib [17%] and in 7 patients who received placebo [8%]). The most common adverse events leading to discontinuation in the sunitinib group were fatigue (in 4% of patients) and diarrhea and cardiac failure (2% each).

The mean relative dose intensity (the proportion of administered doses relative to the number of planned doses at 37.5 mg daily) was 91.3% in the sunitinib group and 100.6% in the placebo group. One or more dose interruptions were reported in 30% and 12% of patients in the sunitinib and placebo groups, respectively. Adverse events were the primary reason for interruptions. Among patients who received sunitinib, the most commonly reported adverse events were neutropenia (in 12% of patients); diarrhea (10%); asthenia, erythrodysesthesia, and hypertension (7% each); and thrombocytopenia (6%). Among the patients who received placebo, the most commonly reported adverse events were abdominal pain, vomiting, and asthenia (each in 3% of patients). At least one dose reduction to 25 mg per day was reported in 31% and 11% of patients receiving sunitinib and placebo, with dose escalations to 50 mg per day in 10% and 24%, respectively.

Sixty-eight patients (31 patients in the sunitinib group and 37 patients in the placebo group) received treatment with a somatostatin analogue either before enrollment (30 patients who received sunitinib and 32 patients who received placebo) or during the study (23 patients who received sunitinib and 25 patients who received placebo), concomitantly with the study drug. Of the patients who had received treatment with a somatostatin analogue before enrollment, 22 of those in the sunitinib group and 20 of those in the placebo group continued the use of the somatostatin analogue during the study. A single patient in the sunitinib group and 5 patients in the placebo group began to receive a somatostatin analogue after study enrollment while they were already receiving a study drug.

EFFICACY

Progression-free Survival

Among the 171 patients enrolled in the study, 81 primary outcome events (disease progression or death) were reported as of April 15, 2009 (Table 2). An improvement in progression-free survival with sunitinib was observed: median, 11.4 months as compared with 5.5 months with placebo (hazard ratio for disease progression or death, 0.42; 95% confidence interval [CI], 0.26 to 0.66; P<0.001) (Fig. 1A). The probability of progression-free survival at 6 months was 71.3% in the sunitinib group and 43.2% in the placebo group. The observed test statistic (z value) was 3.85, which did not exceed the z value of 3.88 (which was adjusted for three assessments of the data by the data-monitoring committee) that constituted the Lan-DeMets and O'Brien-Fleming efficacy boundary for statistical significance. Two sensitivity analyses for progression-free survival were performed, and the results provided support for the robustness of the primary analysis (Table 1 in the Supplementary Appendix).

An exploratory analysis to determine the potential influence of patient and tumor characteristics on treatment effect showed that in all subgroups analyzed, the hazard ratio for progression or death favored sunitinib (Fig. 2). Sunitinib improved progression-free survival as compared with placebo among patients with a Ki-67 index of 5% or less, with a trend toward a benefit among the few patients with a Ki-67 index of more than 5%.

In a multivariate analysis, only the interval between diagnosis and randomization (≥3 years vs. <3 years) was a potential independent prognostic variable for progression-free survival (hazard ratio for progression or death, 0.60; 95% CI, 0.38 to 0.95; P=0.03). The progression-free survival advantage with sunitinib treatment versus placebo was greater with adjustment for the interval between diagnosis and randomization (hazard ratio, 0.37; 95% CI, 0.23 to 0.60; P<0.001).

Overall Survival

Nine deaths were reported in the sunitinib group (10%) and 21 deaths were reported in the placebo group (25%), and most patients were still in follow-up at the data cutoff point. The hazard ratio for death was 0.41 (95% CI, 0.19 to 0.89; P=0.02) in favor of sunitinib. Kaplan-Meier estimates are

Table 2. Summary of Efficacy Measures in the Intention-to-Treat Population.*

Outcome	Sunitinib (N=86)	Placebo (N=85)	P Value
Progression-free survival			
Patients with events — no. (%)	30 (35)	51 (60)	
Type of event — no. (%)			
Progression	27 (31)	48 (56)	
Death without progression	3 (3)	3 (4)	
Patients with data censored — no. (%)	56 (65)	34 (40)	
Probability of being event-free at mo 6 — % (95% CI)	71.3 (60.0–82.5)	43.2 (30.3–56.1)	
Estimated median progression-free survival			
No. of months (95% CI)†	11.4 (7.4–19.8)	5.5 (3.6–7.4)	
Hazard ratio for progression or death (95% CI)	0.42 (0.26–0.66)		<0.001
Overall survival			
Deaths — no. (%)	9 (10)	21 (25)	
Patients with data censored — no. (%)	77 (90)	64 (75)	
Survival probability at mo 6 — % (95% CI)	92.6 (86.3–98.9)	85.2 (77.1–93.3)	
Overall survival			
Estimated median	Not reached	Not reached	
Hazard ratio for death (95% CI)	0.41 (0.19–0.89)		0.02
Objective tumor response			
Best observed RECIST response — no. (%)			
Complete response	2 (2)	0	
Partial response	6 (7)	0	
Stable disease	54 (63)	51 (60)	
Progressive disease	12 (14)	23 (27)	
Could not be evaluated	12 (14)	11 (13)	
Objective response rate — %	9.3	0	0.007

* CI denotes confidence interval, and RECIST Response Evaluation Criteria in Solid Tumors.
† Data for a total of three patients (one in the sunitinib group and two in the placebo group) were censored at day 1 in the primary analysis of progression-free survival because of inadequate baseline tumor assessment, since the protocol required the presence of at least one measurable target lesion at baseline for enrollment eligibility.

shown in Figure 1B and Table 2; because of the relatively high number of censored events, median overall survival could not be estimated for either study group.

Tumor Response

Eight patients who received sunitinib had a confirmed tumor response (two had complete responses and six had partial responses) (Fig. 1C); the objective response rate was 9.3% (95% CI, 3.2 to 15.4). No objective responses were observed with placebo (Fig. 1C) (P=0.007 for the between-group difference) (Table 2). Among patients with a tumor response, seven had nonfunctioning tumors and in one, tumor function was unknown; the median time to tumor response was 3.1 months (range, 0.8 to 11.1). The duration of response ranged from 0.9 to more than 15.0 months. Only one of the eight patients with a response had disease progression before trial closure.

SAFETY

The majority of adverse events in both groups were grade 1 or 2 in severity, with grade 3 or

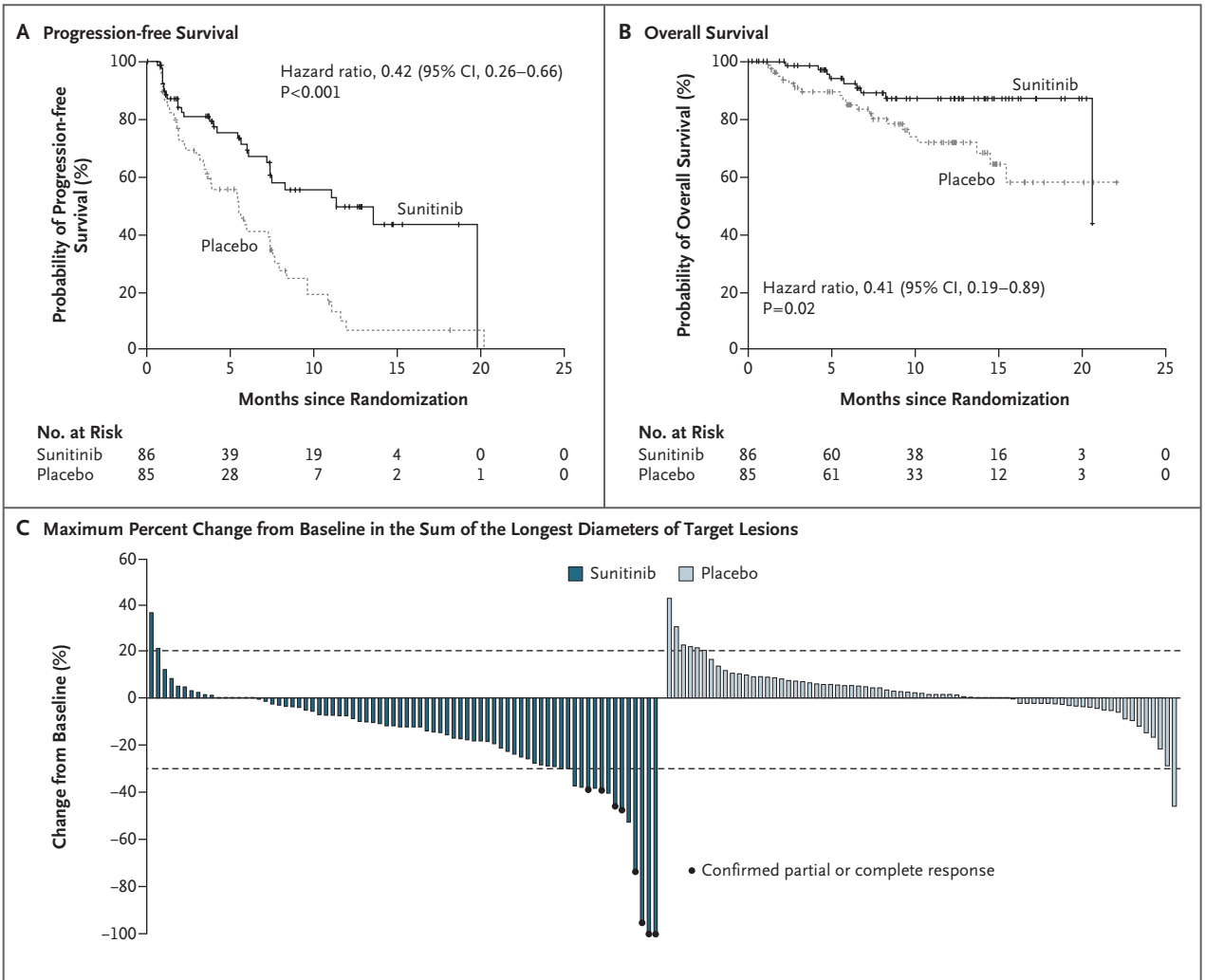

Figure 1. Kaplan-Meier Analysis of Progression-free Survival and Overall Survival in the Intention-to-Treat Population and the Maximum Percent Change from Baseline in the Sum of the Longest Diameters of Target Lesions, According to Patient.

Among 171 patients (86 patients who received sunitinib and 85 patients who received placebo), the median progression-free survival was 11.4 months in the sunitinib group versus 5.5 months in the placebo group (hazard ratio for disease progression or death, 0.42; 95% confidence interval [CI], 0.26 to 0.66; P<0.001) (Panel A). Median overall survival was not reached, but the observed hazard ratio favored sunitinib (0.41; 95% CI, 0.19 to 0.89; P=0.02) (Panel B). Confirmed responses were those that persisted on repeat imaging 4 or more weeks after initial documentation, as assessed by investigators using Response Evaluation Criteria in Solid Tumors[27] (Panel C). For all lesions that were too small to measure, 0 mm was the imputed measurement in the analysis of the change from baseline. One patient receiving placebo had an unconfirmed tumor response.

4 events more common in patients who received sunitinib (Table 3). The most common adverse events associated with sunitinib were diarrhea, nausea, asthenia, vomiting, and fatigue; each occurred in 30% or more of patients. Vomiting, asthenia, and fatigue occurred at similar rates in both groups; abdominal and back pain were more common in patients who received placebo. Palmar-plantar erythrodysesthesia and hypertension of any grade occurred in 23% and 26% of patients receiving sunitinib, respectively. The most common grade 3 or 4 adverse events in patients who received sunitinib were neutropenia (12%) and hypertension (10%).

Hyperthyroidism was reported as an adverse event in two patients who received placebo, and hypothyroidism was reported as an adverse event in six patients who received sunitinib and in one patient who received placebo. All but one of these events were considered to be treatment-related,

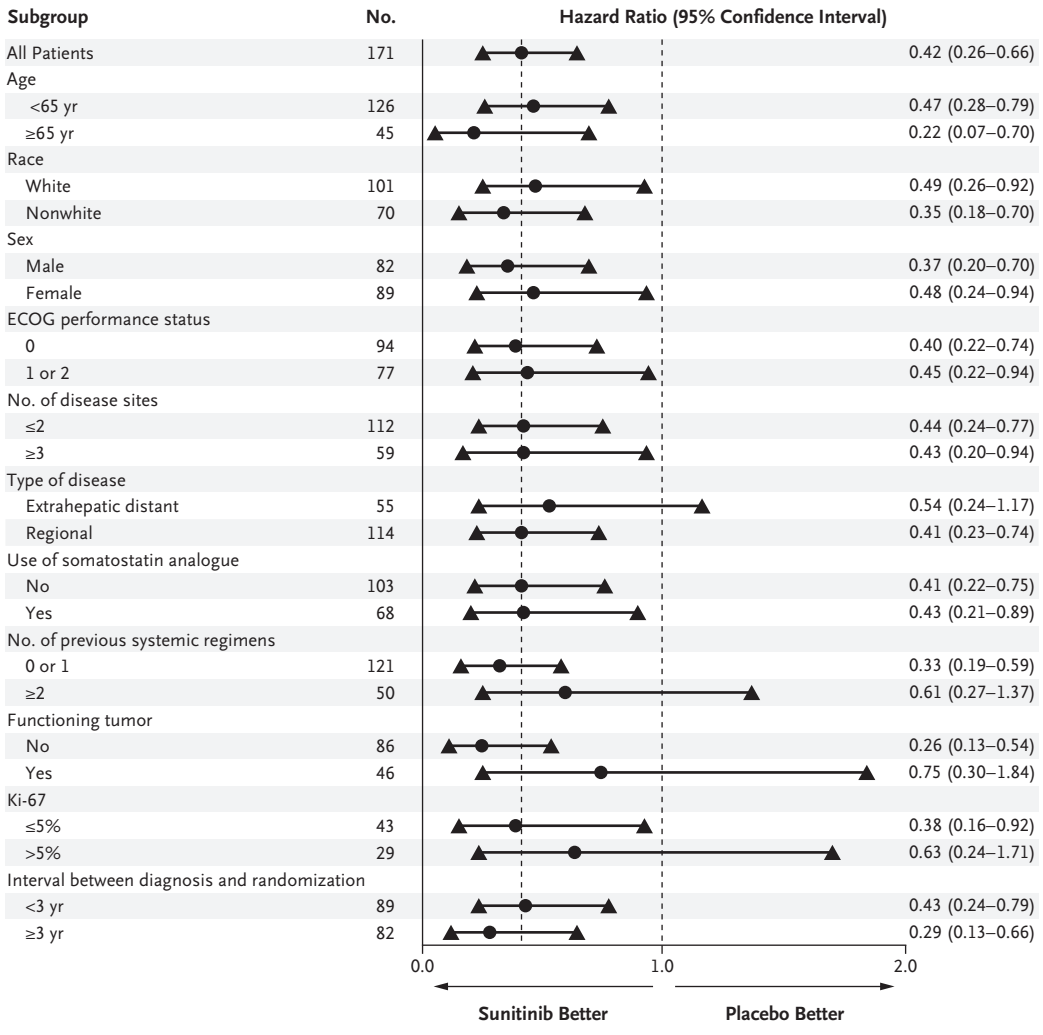

Figure 2. Cox Proportional-Hazards Analysis of Progression-free Survival in Selected Subgroups, According to Baseline Characteristics in the Intention-to-Treat Population.

The Eastern Cooperative Oncology Group (ECOG) grades the status of patients with respect to activities of daily living on a scale of 0 to 5, with 0 indicating that the patient is fully active and 5 indicating death. The category for use of somatostatin analogues includes all patients who received somatostatin analogues at any time before or during the study. The triangles indicate standard errors.

and all were grade 1 or 2 in severity and classified as nonserious. Overall, findings for thyroid function were consistent with those previously reported with the use of sunitinib.

Five patients who received sunitinib and nine patients who received placebo died during the trial period (from the first study-drug dose until 28 days after the last dose). The deaths were attributed to the disease under study, with the exception of grade 5 cardiac failure (in one patient who received sunitinib) and grade 5 dehydration (in one patient who received placebo), which were both considered to be related to the study drug. Other serious adverse events were less common in the sunitinib group than in the placebo group (26% of patients vs. 41%) (Table 2 in the Supplementary Appendix).

QUALITY OF LIFE

EORTC QLQ-C30 data were available for 73 of 86 patients in the sunitinib group and 71 of 85 patients in the placebo group, and they were ana-

Table 3. Common Adverse Events in the Safety Population.*

Event	Sunitinib (N=83)			Placebo (N=82)		
	All Grades	Grade 1 or 2	Grade 3 or 4	All Grades	Grade 1 or 2	Grade 3 or 4
	number of patients (percent)					
Diarrhea	49 (59)	45 (54)	4 (5)	32 (39)	30 (37)	2 (2)
Nausea	37 (45)	36 (43)	1 (1)	24 (29)	23 (28)	1 (1)
Asthenia	28 (34)	24 (29)	4 (5)	22 (27)	19 (23)	3 (4)
Vomiting	28 (34)	28 (34)	0	25 (30)	23 (28)	2 (2)
Fatigue	27 (32)	23 (28)	4 (5)	22 (27)	15 (18)	7 (8)
Hair-color changes	24 (29)	23 (28)	1 (1)	1 (1)	1 (1)	0
Neutropenia	24 (29)	14 (17)	10 (12)	3 (4)	3 (4)	0
Abdominal pain	23 (28)	19 (23)	4 (5)	26 (32)	18 (22)	8 (10)
Hypertension	22 (26)	14 (17)	8 (10)	4 (5)	3 (4)	1 (1)
Palmar–plantar erythrodysesthesia	19 (23)	14 (17)	5 (6)	2 (2)	2 (2)	0
Anorexia	18 (22)	16 (19)	2 (2)	17 (21)	16 (20)	1 (1)
Stomatitis	18 (22)	15 (18)	3 (4)	2 (2)	2 (2)	0
Dysgeusia	17 (20)	17 (20)	0	4 (5)	4 (5)	0
Epistaxis	17 (20)	16 (19)	1 (1)	4 (5)	4 (5)	0
Headache	15 (18)	15 (18)	0	11 (13)	10 (12)	1 (1)
Insomnia	15 (18)	15 (18)	0	10 (12)	10 (12)	0
Rash	15 (18)	15 (18)	0	4 (5)	4 (5)	0
Thrombocytopenia	14 (17)	11 (13)	3 (4)	4 (5)	4 (5)	0
Mucosal inflammation	13 (16)	12 (14)	1 (1)	6 (7)	6 (7)	0
Weight loss	13 (16)	12 (14)	1 (1)	9 (11)	9 (11)	0
Constipation	12 (14)	12 (14)	0	16 (20)	15 (18)	1 (1)
Back pain	10 (12)	10 (12)	0	14 (17)	10 (12)	4 (5)

* Adverse events were defined on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Events listed are those of any grade that occurred in more than 15% of patients in either group.

lyzed for the first 10 cycles. No overall difference was noted between study groups in global health-related quality of life; cognitive, emotional, physical, role, and social functioning; or in other symptoms and scales either at baseline or at any other time point (data not shown), with the exception of diarrhea.

In the repeated-measures, mixed-effects model, patients who received sunitinib had overall clinically and statistically significant worsening of diarrhea (difference, 21.4 points; $P<0.001$), and although statistically significant worsening of insomnia ($P=0.04$) was noted, the overall difference (7.8 points) was not clinically meaningful, with the use of the minimally-important-difference approach, in which a change or between-group difference of less than 10 points is not considered clinically significant.[32]

DISCUSSION

In this randomized trial involving patients with advanced, progressive, well-differentiated pancreatic neuroendocrine tumors, median progression-free survival among patients who received sunitinib was more than twice that among patients who received placebo (11.4 vs. 5.5 months). The improvement in progression-free survival observed among patients who received sunitinib provides support for previous preclinical and clinical data suggesting that neuroendocrine tumors may be particularly sensitive to combined

inhibition of VEGFRs and PDGFR.[21,22,24] The trial was terminated early because of the risk of serious adverse events, disease progression, and death among patients receiving placebo. The objective response rate and overall survival also consistently favored sunitinib. Furthermore, improvement in progression-free survival among patients who received sunitinib, as compared with those who received placebo, was achieved without adversely affecting the quality of life and, per a recently reported post hoc analysis,[33] was associated with a delay in the time to deterioration in the quality of life and emotional and physical functioning.

Although early termination of clinical trials may result in overestimation of the true treatment effect and in lower-than-anticipated numbers of enrolled patients, the magnitude of the observed treatment effect, the consistency of the hazard ratio for disease progression or death in the sensitivity analyses, and the favorable survival data in this trial all provide strong evidence of the clinically meaningful benefit of sunitinib. Moreover, results from a retrospective, blinded, independent central review of imaging studies in 49% of patients in this study (84 of 171 patients) provide support for the findings with respect to investigator-assessed progression-free survival (Fig. 2 in the Supplementary Appendix).

The trial population was relatively unselected, with demographic characteristics and treatment history that are typical of patients with advanced pancreatic neuroendocrine tumors. When we examined outcomes according to baseline characteristics, previous systemic treatment, and prognostic factors in an exploratory subgroup analysis, the benefit of sunitinib extended across all subgroups, although the numbers of patients were small in some subgroups. The efficacy of sunitinib in our trial appears to be similar regardless of the number of previous treatments or previous exposure to somatostatin analogues. In addition, although numerical between-group differences were observed in some baseline characteristics, a post hoc analysis with the use of Fisher's exact test showed no significant differences in these baseline factors (Table 1); moreover, according to univariate and multivariate analysis, these factors had no effect on the progression-free survival benefit (data not shown).

The most frequent adverse events observed with continuous daily administration of sunitinib, including diarrhea, nausea, vomiting, asthenia, and fatigue, were consistent with those observed in previous trials of sunitinib,[24,34] and rates of vomiting, asthenia, and fatigue were similar in the sunitinib and placebo groups in this study. Most sunitinib-related adverse events were manageable through dose interruption or modification.

The incidence of pancreatic neuroendocrine tumors is increasing, and the 5-year survival rate is below 43%.[35,36] Our findings, which show the efficacy of sunitinib in pancreatic neuroendocrine tumors, are particularly important because of the limited number of effective treatment options for advanced disease. Somatostatin analogues,[6,7] peptide-receptor radionuclide therapy,[37,38] and inhibitors of the mammalian target of rapamycin[39] have shown antitumor activity in pancreatic neuroendocrine tumors, and results from a phase 3 trial of everolimus are reported elsewhere in this issue of the *Journal*.[40]

Our data show that rationally designed inhibition of VEGFR and PDGFR signaling with the use of sunitinib, given as a continuous daily dose, resulted in clinically meaningful improvements in progression-free survival, the objective-response rate, and overall survival among patients with pancreatic neuroendocrine tumors.

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