ORIGINAL ARTICLE

Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy

A. Ravaud, R.J. Motzer, H.S. Pandha, D.J. George, A.J. Pantuck, A. Patel, Y.-H. Chang, B. Escudier, F. Donskov, A. Magheli, G. Carteni, B. Laguerre, P. Tomczak, J. Breza, P. Gerletti, M. Lechuga, X. Lin, J.-F. Martini, K. Ramaswamy, M. Casey, M. Staehler, and J.-J. Patard, for the S-TRAC Investigators*

ABSTRACT

BACKGROUND

Sunitinib, a vascular endothelial growth factor pathway inhibitor, is an effective treatment for metastatic renal-cell carcinoma. We sought to determine the efficacy and safety of sunitinib in patients with locoregional renal-cell carcinoma at high risk for tumor recurrence after nephrectomy.

METHODS

In this randomized, double-blind, phase 3 trial, we assigned 615 patients with locoregional, high-risk clear-cell renal-cell carcinoma to receive either sunitinib (50 mg per day) or placebo on a 4-weeks-on, 2-weeks-off schedule for 1 year or until disease recurrence, unacceptable toxicity, or consent withdrawal. The primary end point was disease-free survival, according to blinded independent central review. Secondary end points included investigator-assessed disease-free survival, overall survival, and safety.

RESULTS

The median duration of disease-free survival was 6.8 years (95% confidence interval [CI], 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group (hazard ratio, 0.76; 95% CI, 0.59 to 0.98; P=0.03). Overall survival data were not mature at the time of data cutoff. Dose reductions because of adverse events were more frequent in the sunitinib group than in the placebo group (34.3% vs. 2%), as were dose interruptions (46.4% vs. 13.2%) and discontinuations (28.1% vs. 5.6%). Grade 3 or 4 adverse events were more frequent in the sunitinib group (48.4% for grade 3 events and 12.1% for grade 4 events) than in the placebo group (15.8% and 3.6%, respectively). There was a similar incidence of serious adverse events in the two groups (21.9% for sunitinib vs. 17.1% for placebo); no deaths were attributed to toxic effects.

CONCLUSIONS

Among patients with locoregional clear-cell renal-cell carcinoma at high risk for tumor recurrence after nephrectomy, the median duration of disease-free survival was significantly longer in the sunitinib group than in the placebo group, at a cost of a higher rate of toxic events. (Funded by Pfizer; S-TRAC ClinicalTrials.gov number, NCT00375674.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Ravaud at the Department of Medical Oncology, Hôpital Saint André, 1 rue Jean Burguet, 33075 Bordeaux, France, or at alain.ravaud@chu-bordeaux.fr.

*A complete list of investigators in the Sunitinib as Adjuvant Treatment for Patients at High Risk of Recurrence of Renal Cell Carcinoma Following Nephrectomy (S-TRAC) trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Staehler and Patard contributed equally to this article.

This article was published on October 10, 2016, at NEJM.org.

DOI: 10.1056/NEJMoa1611406

Each year, approximately 300,000 persons worldwide are diagnosed with renal-cell carcinoma, resulting in 129,000 deaths.[1,2] The prognosis for patients with renal-cell carcinoma is dependent on the stage of disease and other risk factors. The 5-year survival rate is 53% for locoregional (stage III) disease and 8% for metastatic disease.[3] Overall, locoregional disease is diagnosed in 16% of patients with renal-cell carcinoma,[4] and up to 40% of these patients have a relapse with metastasis after nephrectomy.[5,6] The relapse risk can be assessed with the use of two validated models, the University of California Los Angeles Integrated Staging System (UISS)[7,8] and the stage, size, grade, and necrosis (SSIGN) score.[9] (Additional details about disease staging are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Although the prognosis for patients with metastatic renal-cell carcinoma has improved in the past decade, no curative treatment is currently available. Several adjuvant strategies, including cytokine therapy, radiotherapy, and hormone therapy, have been explored to decrease the rate of relapse, but none were successful.[6] The proven efficacy of antiangiogenic therapies, including the vascular endothelial growth factor (VEGF) pathway inhibitors sunitinib[10] and sorafenib,[11] in patients with metastatic renal-cell carcinoma[12] supports the evaluation of these drugs as adjuvant therapy.[6] In a previous phase 3 trial (ASSURE) involving patients with locally advanced renal-cell carcinoma, investigators did not find any treatment advantage for adjuvant therapy with sunitinib or sorafenib over placebo.[13] In Sunitinib as Adjuvant Treatment for Patients at High Risk of Recurrence of Renal Cell Carcinoma Following Nephrectomy (S-TRAC), we examined the efficacy and safety of sunitinib versus placebo in preventing relapse in patients with resected locoregional renal-cell carcinoma at high risk for disease recurrence.

METHODS

PATIENTS

From September 19, 2007, to April 7, 2011, we enrolled 615 patients at 99 centers in 21 countries in this prospective, randomized, double-blind, phase 3 trial. Eligible patients were at least 18 years of age and had received a diagnosis of locoregional renal-cell carcinoma (tumor stage 3 or higher, regional lymph-node metastasis, or both) on the basis of modified UISS criteria.[8] Other eligibility criteria included histologic confirmation of clear-cell renal-cell carcinoma, no previous systemic treatment, a score of no more than 2 on the Eastern Cooperative Oncology Group (ECOG) scale (which ranges from 0 to 5, with higher scores indicating greater disability) before nephrectomy, and treatment initiation within 3 to 12 weeks after nephrectomy. The absence of macroscopic residual or metastatic disease after nephrectomy, as confirmed on blinded independent central review of computed tomographic (CT) images, was required before enrollment. Exclusion criteria included renal metastasis or histologically undifferentiated tumors, diagnosis of a second cancer within 5 years before randomization, a major cardiovascular event or disease within 6 months before enrollment, and uncontrolled hypertension (blood pressure, >150/100 mm Hg).

STUDY DESIGN AND OVERSIGHT

Randomization was stratified according to the UISS-defined high-risk group, the ECOG score (<2 vs. 2), and country of residence (Table S1 in the Supplementary Appendix). Patients were assigned in a 1:1 ratio to receive either oral sunitinib (50 mg per day) or placebo on a 4-weeks-on, 2-weeks-off schedule for 1 year. Dose interruptions or dose reductions to 37.5 mg per day were allowed, depending on the type and severity of toxicity. Treatment continued until disease recurrence, diagnosis of a secondary cancer, unacceptable toxic effects, or consent withdrawal.

A separate cohort of patients who were enrolled in China was added after the initiation of the trial to satisfy the regulatory filing in China. Data from the China cohort, which were not mature at the time of the data cutoff, were intended to be analyzed separately and are therefore not included in this report. (Additional details are provided in the Supplementary Appendix.)

The trial was approved by the independent review board or ethics committee at each center and was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and applicable local regulatory requirements and laws. All the patients provided written informed consent. An independent data and safety monitoring com-

mittee regularly reviewed patient safety and efficacy data.

The trial was designed as a collaboration between the sponsor, Pfizer, and the academic authors. Manuscript development was led by the first author. All the authors contributed to drafting of the manuscript and provided final approval to submit the manuscript for publication. Sponsor-funded medical writing support was provided by Engage Scientific Solutions of Envision Pharma Group. The trial protocol and statistical analysis plan are available at NEJM.org. The authors assume responsibility for the accuracy and completeness of the data and vouch for the fidelity of the trial to the protocol.

ASSESSMENTS AND END POINTS

Tumor assessments included CT (≤5-mm slice thickness) or magnetic resonance imaging of the chest, abdomen, pelvis, and other applicable sites, conducted at screening, every 12 weeks during the first 3 years, and every 6 months thereafter until disease recurrence or occurrence of metastasis, whichever was determined first until the time of final analysis. Diagnosis of recurrence was based on centrally confirmed imaging or histologic findings.

The primary end point was the duration of disease-free survival, which was defined as the interval between randomization and the first tumor recurrence, the occurrence of metastasis or a secondary cancer (as assessed by blinded independent central review), or death. Secondary end points included overall survival, safety, and health-related quality of life. Additional analyses are described in the Methods section in the Supplementary Appendix.

The duration of exposure was defined as the period between the first and last dose of sunitinib or placebo, including interruptions in administration, cycle delays, and changes in the scheduled 2-week off-treatment period. Safety assessments included adverse events (classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0), laboratory tests, physical examinations, ECOG scores, vital signs, and 12-lead electrocardiographic assessments. Safety data were collected up to 28 days after the end of treatment.

We evaluated health-related quality of life using the self-administered European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (QLQ-C30) and the European Quality of Life–5 Dimensions (EQ-5D) questionnaire, which were completed on day 1 of each treatment cycle and at the end of treatment. A difference of 10 points or more on the QLQ-C30 (which ranges from 0 to 100) between treatments was considered to be clinically meaningful.[14,15] (Higher scores on the QLQ-C30 functional scale and global health status indicate better functioning, whereas higher scores on the symptom scale or higher single-item scores indicate a worsening of symptoms.) Such changes with clinical implications were 0.06 to 0.09 points on the EQ-5D (which ranges from −0.11 to 1.00, with higher scores indicating better health status) and 7 to 12 points on the EQ–Visual Analogue Scale (EQ-VAS, the second part of the EQ questionnaire, which ranges from 0 to 100, with higher scores indicating a better health-related quality of life).[16]

We collected whole-blood and tumor specimens to analyze genetic polymorphisms associated with renal-cell carcinoma and the expression of tissue biomarkers and to test their association with treatment outcomes. The results of biomarker analyses are not included in this report.

STATISTICAL ANALYSIS

We determined that 320 events of recurrence, diagnosis of a second cancer, or death would provide a power of 90% to detect a hazard ratio of 0.69 for the comparison between sunitinib and placebo at a two-sided significance level of 0.05. Since there was a lower-than-expected rate of disease-free survival during the trial, the protocol was amended to specify that the final analysis would occur approximately 5 years after the last patient underwent randomization. It was estimated that approximately 258 events would have occurred at that time, which would provide a power of 84% to detect statistical significance for a hazard ratio of 0.69. (Additional details are provided in the Methods section in the Supplementary Appendix.)

The intention-to-treat population included all the patients who underwent randomization and was the primary population for evaluating all efficacy end points and patient characteristics. We compared the time-to-event end points using a two-sided log-rank test stratified according to UISS high-risk group (Table S1 in the Supplementary Appendix). We used Kaplan–Meier methods to determine the median durations of disease-

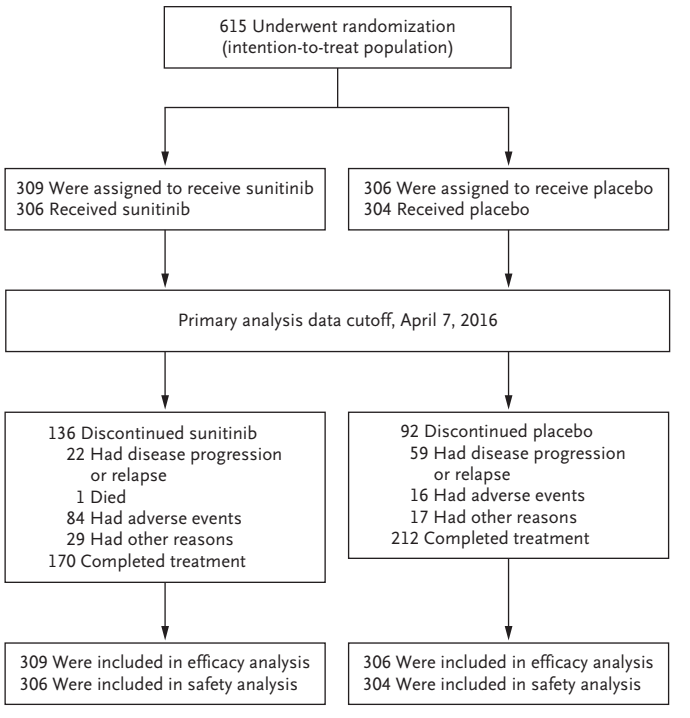

Figure 1. Enrollment and Outcomes.

Among the patients who discontinued either sunitinib or placebo, other listed reasons for discontinuation included a deterioration in health status, loss to follow-up, protocol violation, a reason other than an adverse event, and an unknown reason.

free survival and overall survival with 95% confidence intervals.

Safety data were summarized descriptively for all patients who received at least 1 dose of sunitinib or placebo. QLQ-C30 subscales and single-item subscores were summarized according to the mean and median for each group and plotted according to time. Scores on the EQ-5D and EQ–VAS were reported as means and standard deviations. We used a repeated-measures analysis with a mixed-effects model with treatment, time, treatment according to time, and baseline as covariates to estimate the mean difference in health-related quality of life in the two groups. All statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

PATIENTS

Of the 615 patients who underwent randomization, 309 were assigned to receive sunitinib and 306 to receive placebo. Of these patients, 306 received sunitinib and 304 received placebo; 5 patients did not receive a study drug either because of withdrawal of consent (3 in the sunitinib group) or because of evidence of metastasis (2 in the placebo group) (Fig. 1). The characteristics of the patients were well balanced in the two groups at baseline (Table 1). The median duration of follow-up was 5.4 years (95% confidence interval [CI], 5.2 to 5.6) in the sunitinib group and 5.4 years (95% CI, 5.3 to 5.6) in the placebo group.

As of the data cutoff on April 7, 2016, all the patients had either completed or otherwise discontinued treatment. Data with respect to drug discontinuations and doses are provided in Table S2 in the Supplementary Appendix. The rates of treatment completion were 55.6% for sunitinib and 69.4% for placebo. The median treatment durations were similar, with 12.4 months (range, 0.1 to 14.9) for sunitinib and 12.4 months (range, 0.03 to 13.7) for placebo. Among the patients in the sunitinib group, 54.2% maintained the starting dose (50 mg per day); the median daily dose was 45.9 mg (range, 8.9 to 52.6) in the sunitinib group and 50 mg (6.7 to 52.8) in the placebo group.

EFFICACY

Disease-free Survival

On the basis of blinded independent central review, the median duration of disease-free survival was 6.8 years (95% CI, 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group (hazard ratio, 0.76; 95% CI, 0.59 to 0.98; P=0.03) (Table 2 and Fig. 2). At the time of data cutoff, an event of disease recurrence, a second cancer, or death had occurred in 113 of 309 patients (36.6%) in the sunitinib group and in 144 of 306 patients (47.1%) in the placebo group. At 3 years, the proportions of patients who were disease-free were 64.9% in the sunitinib group and 59.5% in the placebo group; at 5 years, the proportions were 59.3% and 51.3%, respectively.

On the basis of investigator review, an event of disease recurrence, a second cancer, or death had occurred in 132 patients (42.7%) in the sunitinib group and 158 (51.6%) in the placebo group over the trial period. The median duration of investigator-assessed disease-free survival was 6.5 years (95% CI, 4.7 to 7.0) in the sunitinib group and 4.5 years (95% CI, 3.8 to 5.9) in the

Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Sunitinib (N=309)	Placebo (N=306)
Age — yr		
Median (range)	57.0 (25–83)	58.0 (21–82)
18–64	233 (75.4)	224 (73.2)
≥65	76 (24.6)	82 (26.8)
Sex — no. (%)		
Male	222 (71.8)	229 (74.8)
Female	87 (28.2)	77 (25.2)
Race — no. (%)†		
White	254 (82.2)	263 (85.9)
Black	3 (1.0)	1 (0.3)
Asian	43 (13.9)	33 (10.8)
Other	9 (2.9)	9 (2.9)
Median interval from diagnosis to randomization (range) — wk	10.7 (5.1–53.4)	10.7 (3.7–19.9)
Affected kidney at diagnosis — no. (%)		
Right	165 (53.4)	148 (48.4)
Left	144 (46.6)	158 (51.6)
ECOG score — no. (%)		
0	228 (73.8)	220 (71.9)
1	79 (25.6)	84 (27.5)
≥2	1 (0.3)	0
Unknown	1 (0.3)	2 (0.7)
UISS risk group — no. (%)		
A: stage 3 tumor, no or undetermined nodal involvement, no metastasis‡	280 (90.6)	278 (90.8)
A1: low-risk§	115 (37.2)	112 (36.6)
A2: high-risk¶	165 (53.4)	166 (54.2)
B: stage 4 tumor, no or undetermined nodal involvement, no metastasis‡	4 (1.3)	4 (1.3)
C: any tumor stage, locoregional nodal involvement, no metastasis‡	25 (8.1)	24 (7.8)

* There were no significant differences between the two groups. ECOG denotes Eastern Cooperative Oncology Group, and UISS UCLA Integrated Staging System. Percentages may not total 100 because of rounding.
† Race was reported by the investigator.
‡ This category includes any Fuhrman grade (on a scale of 1 to 4, with grade 1 indicating the least atypia and grade 4 the most) and any ECOG score.
§ Low-risk A1 disease includes any Fuhrman grade and an ECOG score of 0 or Fuhrman grade 1 and an ECOG score of 1 or higher.
¶ High-risk A2 disease includes Fuhrman grade 2 or higher and an ECOG score of 1 or higher.

placebo group, but the between-group difference was not significant (hazard ratio, 0.81; 95% CI, 0.64 to 1.02; P=0.08) (Table 2). These results were supported by an analysis of disease-free survival in a subgroup of patients at higher risk than the overall study population, which was defined as tumor stage 3, no or undetermined nodal involvement, no metastasis, Fuhrman grade 2 or more (on a scale of 1 to 4, with grade 1 indicating the least atypia and grade 4 the most), and an ECOG score of 1 or more or tumor stage 4, local nodal involvement, or both. In this subgroup, the dif-

Table 2. Median Duration of Disease-free Survival in Primary and Secondary Analyses.*

Analysis	Sunitinib (N=309)	Placebo (N=306)	Hazard Ratio (95% CI)
	yr (95% CI)		
All patients in central review: primary analysis	6.8 (5.8–NR)	5.6 (3.8–6.6)	0.76 (0.59–0.98)†
Secondary analysis			
All patients in investigator review	6.5 (4.7–7.0)	4.5 (3.8–5.9)	0.81 (0.64–1.02)
Higher-risk patients in central review‡	6.2 (4.9–NR)	4.0 (2.6–6.0)	0.74 (0.55–0.99)†
Higher-risk patients in investigator review‡	5.9 (4.4–7.0)	3.9 (2.8–5.6)	0.76 (0.58–1.01)

* CI denotes confidence interval, and NR not reached.
† P<0.05 for comparison with placebo.
‡ This category includes patients at higher risk than the overall study population, which was defined as those with a stage 3 tumor, no or undetermined nodal involvement, no metastasis, Fuhrman grade 2 or higher, and an ECOG score of 1 or higher or a stage 4 tumor, local nodal involvement, or both. Subgroup analyses did not have the statistical power to determine between-group differences.

ference in disease-free survival was significant on the basis of independent central review (hazard ratio, 0.74; 95% CI, 0.55 to 0.99; P=0.04) but not on the basis of investigator review (hazard ratio, 0.76; 95% CI, 0.58 to 1.01; P=0.06) (Table 2).

There was a high concordance in the assessments of disease-free survival according to blinded independent central review and investigator review, with a low event disagreement in the two groups (11.3% for sunitinib vs. 8.5% for placebo). However, investigators called relapse earlier than the blinded independent central review more often for sunitinib than for placebo, as is represented by the early and late discordance rates (Table S3 in the Supplementary Appendix).

Overall Survival

Data for overall survival, a secondary end point, were not mature at the time of the data cutoff, with deaths reported in 64 patients (20.7%) in the sunitinib group and 64 (20.9%) in the placebo group. The median overall survival was not reached in either group, and the hazard ratio for the comparison between sunitinib and placebo was 1.01 (95% CI, 0.72 to 1.44; P=0.94) (Fig. S1 in the Supplementary Appendix).

SAFETY

Treatment-emergent adverse events occurred in 99.7% of the patients in the sunitinib group and in 88.5% of those in the placebo group, whereas adverse events that investigators attributed to treatment occurred in 98.4% and 75.7%, respectively. The most common all-cause adverse events in the sunitinib group were diarrhea, palmar–plantar erythrodysesthesia, hypertension, fatigue, and nausea (Table 3, and Table S4 in the Supplementary Appendix); the most common adverse events that investigators attributed to treatment were diarrhea, palmar–plantar erythrodysesthesia, fatigue, hypertension, and mucosal inflammation (Table S5 in the Supplementary Appendix). Adverse events of grade 3 or higher were reported in 194 patients (63.4%) in the sunitinib group and in 66 (21.7%) in the placebo group; grade 5 events occurred in 5 patients (1.6%) in each group. The rates of serious adverse events were similar (21.9% and 17.1%, respectively) (Table S6 in the Supplementary Appendix).

Dose reductions or interruptions because of adverse events occurred in 34.3% and 46.4%, respectively, of the patients in the sunitinib group and in 2.0% and 13.2% in the placebo group. Treatment discontinuations owing to adverse events occurred in 86 patients (28.1%) in the sunitinib group and 17 (5.6%) in the placebo group (Table S7 in the Supplementary Appendix). Renal-cell carcinoma was the most common cause of death in the two groups and accounted for 47 of 62 deaths (75.8%) in the sunitinib group and for 47 of 64 (73.4%) in the placebo group. No deaths were attributed to toxic effects related to a study treatment.

HEALTH-RELATED QUALITY OF LIFE

In the two groups, the rates of response to QLQ-C30 and EQ-5D were high (>90% completion of questionnaires at the beginning of each

cycle and >78% at the end-of-treatment assessment). On most QLQ-C30 subscales, patients in the sunitinib group had lower scores than those in the placebo group. However, the estimated mean differences, while significant, did not reach the prespecified minimally important difference of 10 points, with the exception of diarrhea (mean difference, 12.0 points; 95% CI, 9.6 to 14.4) and loss of appetite (mean difference, 10.0 points; 95% CI, 7.9 to 12.2; P<0.001 for both comparisons). Similarly, patients in the sunitinib group had significantly lower scores on the EQ-5D and EQ-VAS than did those in the placebo group, although the differences did not reach the minimally important difference (Table S7 in the Supplementary Appendix).

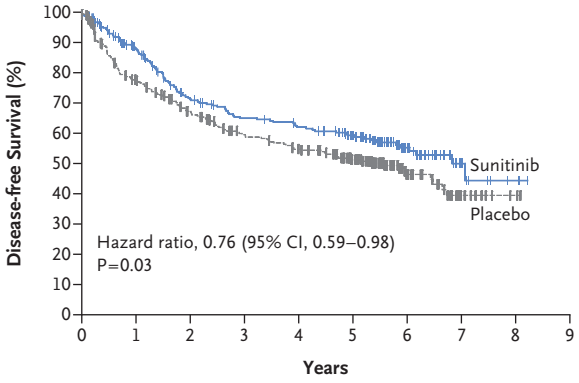

Figure 2. Disease-free Survival.

The median duration of disease-free survival according to independent central review was 6.8 years (95% confidence interval [CI], 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group. At the time of data cutoff, an event of disease recurrence, a second cancer, or death had occurred in 113 of 309 patients (36.6%) in the sunitinib group and in 144 of 306 patients (47.1%) in the placebo group.

DISCUSSION

Up to 40% of patients with locoregional renal-cell carcinoma have a relapse with metastasis after nephrectomy.[5,6] There are limited data to show that adjuvant therapy can reduce the risk of relapse, and standard management is limited to surveillance. In this trial, we found that patients in the sunitinib group had a longer median duration of disease-free survival than did those in the placebo group (6.8 years vs. 5.6 years), as determined by blinded independent central review. The benefit crossed the prespecified boundary for significance at the time of the final analysis. Disease-free survival curves separated early and remained separated over the course of the trial. The period of follow-up in our trial (median, 5.4 years) was similar to that in the ASSURE trial (median, 5.8 years).[13] However, since the life expectancy after nephrectomy in this population of patients is nearly 40% at 10 years,[17] further study is needed to confirm whether the effect of adjuvant sunitinib treatment is maintained in the long term. At 5 years, the proportion of patients who were disease-free was 8.0 percentage points higher with sunitinib than with placebo, which suggests that the effect of 1 year of adjuvant treatment with sunitinib is maintained over time.

The safety profile of adjuvant sunitinib was consistent with the broad experience observed in patients undergoing treatment for metastatic renal-cell carcinoma.[16,18] The rate of discontinuation because of adverse events among patients in the sunitinib group (28.1%) was higher than that reported in the pivotal trial (8%) comparing sunitinib with interferon alfa in patients with metastatic renal-cell carcinoma.[19] In our trial, skin toxicity (palmar–plantar erythrodysesthesia), hypertension, and fatigue were among the most commonly reported adverse events of grade 3 or higher in the sunitinib group; likewise, these events are commonly reported in sunitinib trials involving patients with metastatic disease.[13,19,20] However, in our trial, skin toxicity of grade 3 or higher was more frequent among patients receiving adjuvant therapy than in those with metastatic disease (16% vs. 5%).[13,19] Overall, these results are consistent with the observation that although the type and incidence of adverse events may not differ greatly between these two patient populations, the events may be less acceptable among patients who have undergone nephrectomy.[6]

Sunitinib-treated patients had significantly lower scores for health-related quality of life than did those in the placebo group while they were receiving active treatment. Differences of 10 to 20 points on the QLQ-C30 subscales have been reported to correspond to a moderate quality-of-life change,[14,15] and generally, a 10-point change is widely accepted as clinically meaningful across various types of cancer. In our trial, only lower scores for diarrhea and loss of appetite — both of which are well-known side effects of VEGF-

Table 3. Adverse Events (Safety Population).*

Event	Sunitinib (N=306)			Placebo (N=304)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	305 (99.7)	148 (48.4)	37 (12.1)	269 (88.5)	48 (15.8)	11 (3.6)
Diarrhea	174 (56.9)	12 (3.9)	0	65 (21.4)	1 (0.3)	0
Palmar–plantar erythrodysesthesia	154 (50.3)	46 (15.0)	3 (1.0)	31 (10.2)	1 (0.3)	0
Hypertension	113 (36.9)	24 (7.8)	0	36 (11.8)	3 (1.0)	1 (0.3)
Fatigue	112 (36.6)	13 (4.2)	2 (0.7)	74 (24.3)	4 (1.3)	0
Nausea	105 (34.3)	6 (2.0)	0	42 (13.8)	0	0
Dysgeusia	103 (33.7)	0	0	18 (5.9)	0	0
Mucosal inflammation	103 (33.7)	14 (4.6)	0	25 (8.2)	0	0
Dyspepsia	82 (26.8)	4 (1.3)	0	19 (6.3)	0	0
Stomatitis	81 (26.5)	5 (1.6)	2 (0.7)	13 (4.3)	0	0
Neutropenia	72 (23.5)	23 (7.5)	3 (1.0)	2 (0.7)	0	0
Asthenia	69 (22.5)	11 (3.6)	0	37 (12.2)	2 (0.7)	1 (0.3)
Hair-color change	68 (22.2)	0	0	7 (2.3)	0	0
Thrombocytopenia	64 (20.9)	15 (4.9)	4 (1.3)	5 (1.6)	1 (0.3)	0
Decreased appetite	59 (19.3)	2 (0.7)	0	16 (5.3)	0	0
Rash	59 (19.3)	2 (0.7)	0	29 (9.5)	0	0
Vomiting	58 (19.0)	7 (2.3)	0	20 (6.6)	0	0
Headache	57 (18.6)	2 (0.7)	0	36 (11.8)	0	0
Hypothyroidism	56 (18.3)	0	0	4 (1.3)	0	0
Epistaxis	55 (18.0)	0	0	9 (3.0)	0	0

* Listed are adverse events that were reported in at least 15% of the patients in each group during treatment. Grade 5 events occurred in 5 patients (1.6%) in each group. Patients were counted once at the highest grade with respect to common terminology criteria during the study. A complete listing of adverse events is provided in Table S4 in the Supplementary Appendix.

pathway inhibitors[16,18] — were clinically meaningful.[14,15]

In the ASSURE trial, there was no improvement in disease-free survival in patients receiving sunitinib or sorafenib as compared with placebo, including in subgroups of patients with clear-cell histologic results or high-risk (tumor stage 3 or 4) disease.[13] Distinct patient populations, dose regimens, and trial methods are likely to be responsible for the different outcomes in the two trials. For example, the ASSURE trial included many patients with early (stage 1) tumors (9%) and patients with non–clear-cell histologic results (21%), whereas our trial was designed to include only patients with late-stage (locoregional), clear-cell renal-cell carcinoma. In the ASSURE trial, the starting dose of sunitinib was changed midtrial, from 50 mg to 37.5 mg, with subgroup analysis showing a trend toward a shorter duration of disease-free survival for those who initiated treatment at 37.5 mg; furthermore, dose reductions to 25 mg were allowed. In contrast, sunitinib was administered at 50 mg in our trial, with dose reduction allowed to 37.5 mg per day but not 25 mg per day. In addition, in our trial, disease-free status before enrollment was confirmed by central review of radiographs, and the primary end point of disease-free survival was based on blinded central review. In the ASSURE trial, both assessments were performed by investigators only.

In conclusion, patients with locoregional renal-cell carcinoma at high risk for tumor recurrence after nephrectomy who were receiving adjuvant treatment with sunitinib had a longer duration of disease-free survival than did those

receiving placebo. The safety profile in patients treated with adjuvant sunitinib revealed moderate declines in quality of life while receiving active treatment.

Supported by Pfizer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Memorial Sloan Kettering Cancer Center for providing partial support for the patients' treatment through a core grant from the National Cancer Institute; and Jaya Vas, Ph.D., at Engage Scientific Solutions for medical writing support.

APPENDIX

The authors' full names and academic degrees are as follows: Alain Ravaud, M.D., Ph.D., Robert J. Motzer, M.D., Hardev S. Pandha, M.D., Ph.D., Daniel J. George, M.D., Allan J. Pantuck, M.D., Anup Patel, M.S., F.R.C.S., Yen-Hwa Chang, M.D., Ph.D., Bernard Escudier, M.D., Frede Donskov, M.D., Ph.D., Ahmed Magheli, M.D., Ph.D., Giacomo Carteni, M.D., Brigitte Laguerre, M.D., Piotr Tomczak, M.D., Jan Breza, M.D., Ph.D., Paola Gerletti, B.Sc.D., Mariajose Lechuga, M.D., Xun Lin, Ph.D., Jean-Francois Martini, Ph.D., Krishnan Ramaswamy, Ph.D, Michelle Casey, Ph.D., Michael Staehler, M.D., Ph.D., and Jean-Jacques Patard, M.D., Ph.D.

The authors' affiliations are as follows: the Department of Medical Oncology, Bordeaux University Hospital, Bordeaux (A.R.), Department of Medical Oncology, Institut Gustave Roussy, Villejuif (B.E.), Medical Oncology, Centre Eugene Marquis, Rennes (B.L.), and Department of Urology, Bicêtre Hospital, Paris-Saclay University, Le Kremlin Bicêtre (J.-J.P.) — all in France; Department of Medicine, Memorial Sloan Kettering Cancer Center (R.J.M.), and Pfizer (K.R.) — both in New York; Department of Clinical and Experimental Medicine, University of Surrey, Surrey, United Kingdom (H.S.P.); Division of Medical Oncology, Duke Cancer Institute, Durham, NC (D.J.G.); Department of Urology, Ronald Reagan UCLA Medical Center, Los Angeles (A.J.P.), and Pfizer, La Jolla (X.L., J.-F.M.) — both in California; Spire Roding Hospital, London (A.P.); Department of Urology, Taipei Veterans General Hospital, Taipei, Taiwan (Y.-H.C.); Department of Oncology, Aarhus University Hospital, Aarhus, Denmark (F.D.); Department of Urology, Charité Universitätsmedizin Berlin, Berlin (A.M.), and Department of Urology, University Hospital of Munich, Munich (M.S.) — both in Germany; Divisions of Oncology and Urology, Azienda Ospedaliera di Rilievo Nazionale A. Cardarelli, Naples, Italy (G.C.); Klinika Onkologii Oddzial Chemioterapii, Poznan, Poland (P.T.); Department of Urology, Slovak Medical University, Bratislava, Slovakia (J.B.); and Pfizer, Milan (P.G., M.L.), and Collegeville, PA (M.C.).

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359-86.
2. National Comprehensive Cancer Network. Kidney cancer: NCCN guidelines for patients, version 1.2015. 2016 (https://www.nccn.org/patients/guidelines/kidney/index.html).
3. American Cancer Society. Kidney cancer (adult) — renal cell carcinoma. 2014 (http://www.cancer.org/acs/groups/cid/documents/webcontent/003107-pdf.pdf).
4. SEER stat facts sheets: kidney and renal pelvis cancer. National Cancer Institute, 2016 (http://seer.cancer.gov/statfacts/html/kidrp.html).
5. Janzen NK, Kim HL, Figlin RA, Belldegrun AS. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin North Am 2003;30:843-52.
6. Janowitz T, Welsh SJ, Zaki K, Mulders P, Eisen T. Adjuvant therapy in renal cell carcinoma-past, present, and future. Semin Oncol 2013;40:482-91.
7. Zisman A, Pantuck AJ, Dorey F, et al. Improved prognostication of renal cell carcinoma using an integrated staging system. J Clin Oncol 2001;19:1649-57.
8. Patard J-J, Kim HL, Lam JS, et al. Use of the University of California Los Angeles Integrated Staging System to predict survival in renal cell carcinoma: an international multicenter study. J Clin Oncol 2004;22:3316-22.
9. Leibovich BC, Blute ML, Cheville JC, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. Cancer 2003;97:1663-71.
10. Sutent (sunitinib malate). New York: Pfizer, 2006 (package insert) (http://labeling.pfizer.com/showlabeling.aspx?id=607).
11. Nexavar (sorafenib). Wayne, NJ: Bayer HealthCare Pharmaceuticals, 2010 (package insert).
12. Thomas JS, Kabbinavar F. Metastatic clear cell renal cell carcinoma: a review of current therapies and novel immunotherapies. Crit Rev Oncol Hematol 2015;96:527-33.
13. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet 2016;387:2008-16.
14. King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. Qual Life Res 1996;5:555-67.
15. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139-44.
16. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:70.
17. Giberti C, Oneto F, Martorana G, Rovida S, Carmignani G. Radical nephrectomy for renal cell carcinoma: long-term results and prognostic factors on a series of 328 cases. Eur Urol 1997;31:40-8.
18. Eisen T, Sternberg CN, Robert C, et al. Targeted therapies for renal cell carcinoma: review of adverse event management strategies. J Natl Cancer Inst 2012;104:93-113.
19. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115-24.
20. Gore ME, Szczylik C, Porta C, et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. Br J Cancer 2015;113:12-9.