

Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma

Robert J. Motzer, Naomi B. Haas, Frede Donskov, Marine Gross-Goupil, Sergei Varlamov, Evgeny Kopyltsov, Jae Lyun Lee, Bohuslav Melichar, Brian I. Rini, Toni K. Choueiri, Milada Zemanova, Lori A. Wood, M. Neil Reaume, Arnulf Stenzl, Simon Chowdhury, Ho Yeong Lim, Ray McDermott, Agnieszka Michael, Weichao Bao, Marlene J. Carrasco-Alfonso, Paola Aimone, Maurizio Voi, Christian Doehn, Paul Russo, and Cora N. Sternberg, on behalf of the PROTECT investigators

Author affiliations and support information (if applicable) appear at the end of this article.

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Corresponding author: Robert J. Motzer, MD, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065; e-mail: motzerr@mskcc.org.

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A B S T R A C T

Purpose

This phase III trial evaluated the efficacy and safety of pazopanib versus placebo in patients with locally advanced renal cell carcinoma (RCC) at high risk for relapse after nephrectomy.

Patients and Methods

A total of 1,538 patients with resected pT2 (high grade) or \geq pT3, including N1, clear cell RCC were randomly assigned to pazopanib or placebo for 1 year; 403 patients received a starting dose of 800 mg or placebo. To address toxicity attrition, the 800-mg starting dose was lowered to 600 mg, and the primary end point analysis was changed to disease-free survival (DFS) for pazopanib 600 mg versus placebo ($n = 1,135$). Primary analysis was performed after 350 DFS events in the intent-to-treat (ITT) pazopanib 600 mg group (ITT_{600mg}), and DFS follow-up analysis was performed 12 months later. Secondary end point analyses included DFS with ITT pazopanib 800 mg (ITT_{800mg}) and safety.

Results

The primary analysis results of DFS ITT_{600mg} favored pazopanib but did not show a significant improvement over placebo (hazard ratio [HR], 0.86; 95% CI, 0.70 to 1.06; $P = .165$). The secondary analysis of DFS in ITT_{800mg} ($n = 403$) yielded an HR of 0.69 (95% CI, 0.51 to 0.94). Follow-up analysis in ITT_{600mg} yielded an HR of 0.94 (95% CI, 0.77 to 1.14). Increased ALT and AST were common adverse events leading to treatment discontinuation in the pazopanib 600 mg (ALT, 16%; AST, 5%) and 800 mg (ALT, 18%; AST, 7%) groups.

Conclusion

The results of the primary DFS analysis of pazopanib 600 mg showed no benefit over placebo in the adjuvant setting.

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INTRODUCTION

Approximately 75% of patients diagnosed with renal cell carcinoma (RCC) have localized disease where surgical resection of the primary tumor is the current standard of care.^{1,2} Using the stage, size, grade, and necrosis (SSIGN) score, the 5-year relapse rate for intermediate- and high-risk RCC after nephrectomy is predicted to be 30% to 40%.² The identification of adjuvant therapy is an unmet need for locally advanced RCC. Cytokines and girentuximab showed no improvement in disease-free survival (DFS).³⁻⁵ However, these agents demonstrated low antitumor activity in

advanced RCC. Antiangiogenic agents including pazopanib and sunitinib demonstrated clinical efficacy for patients with advanced RCC and are the mainstays of first-line therapy.⁶ The study of antiangiogenic drugs in the adjuvant setting was warranted with the intent of preventing disease recurrence and improving DFS. One phase III study (ASSURE [Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma]) conducted in patients with RCC at intermediate or high risk of relapse failed to demonstrate an improvement in DFS with adjuvant sunitinib or sorafenib.⁷ Recently, a significant improvement in DFS was reported from the phase III S-TRAC (Sunitinib Treatment of Renal Adjuvant Cancer) study, which

ASSOCIATED CONTENT



See accompanying Editorial on page 3895



Appendix
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Data Supplement
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evaluated the efficacy of adjuvant sunitinib in high-risk RCC after nephrectomy.⁸

Pazopanib demonstrated a positive benefit-risk ratio in patients with advanced RCC and has received regulatory approval as first-line treatment.⁹⁻¹¹ PROTECT (Pazopanib As Adjuvant Therapy in Localized/Locally Advanced RCC After Nephrectomy [VEG113387]) evaluated the efficacy and safety of pazopanib as an adjuvant therapy for patients with locally advanced RCC at high risk of relapse after nephrectomy. The trial was initiated using 800 mg of pazopanib versus placebo. However, to address intolerance and toxicity attrition, the 800-mg starting dose was lowered to 600 mg, and the primary end point analysis changed to DFS for the 600-mg cohort.

PATIENTS AND METHODS

Patients

Eligible patients were age ≥ 18 years and had resected nonmetastatic (M0) clear-cell or predominant clear-cell RCC histology, fulfilling any of the following combinations of pathologic staging based on TNM classification per the American Joint Committee on Cancer (2010 version) and Fuhrman nuclear grades: pT2G3-4N0, pT3-T4 G_{any}N0, or pT_{any}G_{any}N1. Baseline imaging assessment by independent radiologist review excluded metastasis. Patients had Karnofsky performance score of ≥ 80 and adequate organ function. Exclusion criteria are detailed in the Appendix (online only).

Study Design

Patients were stratified by: partial versus radical nephrectomy and TNM staging per the American Joint Committee on Cancer (2010 version) and Fuhrman nuclear grades (pT2G3-G4N0, pT3G_{any}N0, pT4G_{any}N0, or pT_{any}G_{any}N1). Patients were randomly assigned at a one-to-one ratio to receive pazopanib or matching placebo for 1 year. The study was designed with pazopanib 800 mg once daily as the starting dose; however, the initial dose was subsequently reduced to 600 mg once daily because the treatment discontinuation rate was higher than expected based on blinded aggregate safety review. The decision to change the primary end point analysis of this study was taken jointly by the sponsor and the study steering committee. After the first 8 to 12 weeks of treatment, the dose could be maintained or escalated to 800 mg daily, based on a patient's safety and tolerability. Assessments for recurrence and safety were performed at regular intervals (Appendix). Dose adjustments and treatment discontinuation based on adverse events (AEs) occurred according to protocol guidelines (Appendix).

Study Oversight

The study was approved by local institutional review boards and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. The study was a collaboration of the authors and the sponsor (Novartis/GlaxoSmithKline).

End Points and Assessments

The primary end point was investigator-assessed DFS (independent review was used for eligibility but not for assessment of primary end point), defined as time from random assignment to development of local disease recurrence and/or metastasis or death resulting from any cause. The primary objective was to evaluate DFS with pazopanib 600 mg. Secondary objectives were to evaluate overall survival (OS), defined as time from random assignment to death resulting from any cause; DFS rates at yearly time points; DFS and OS with pazopanib 800 mg daily as initial dose compared with placebo; safety; and measures of patient-reported health

outcomes and quality of life. Details of the quality-of-life health outcome assessments are provided in the Appendix.

Statistical Analysis

PROTECT was originally designed to evaluate pazopanib at a starting dose of 800 mg daily. The sample size was estimated to allow 85% power to detect a 23% reduction in disease-recurrence risk (hazard ratio [HR], 0.77). The overall 1-, 3-, and 5-year DFS rates for patients receiving placebo were assumed to be 70%, 54%, and 49%, respectively. Later, the pazopanib dose was amended to a lower starting dose (600 mg daily). The choice of 600 mg was based on the dose used for first dose reduction from 800 mg in a large phase III study in advanced RCC.¹² The study sample size was re-estimated to allow 85% power to detect a 30% reduction in disease-recurrence risk with pazopanib 600 mg daily as initial dose compared with placebo (HR, 0.70). The assumptions of the overall 1-, 3-, and 5-year DFS rates for patients receiving placebo were changed to 77%, 63%, and 54%, respectively. A total of 319 DFS events were needed, which required 1,100 patients (550 per treatment arm) to be enrolled. The total study enrollment was 1,538 patients; 403 patients were randomly assigned to the 800 mg daily starting dose (pazopanib, n = 198; placebo, n = 205), and 1,135 patients were randomly assigned to the 600 mg daily starting dose (pazopanib, n = 571; placebo, n = 564). The primary analysis was conducted when 350 events had occurred (data cutoff, October 15, 2015), and the DFS follow-up analysis was conducted with a data cutoff of October 15, 2016.

The primary analysis group for efficacy included all randomly assigned patients who received a starting dose of 600 mg daily or placebo, designated as the intent-to-treat pazopanib 600 mg group (ITT_{600mg}). Two secondary groups were analyzed for efficacy: ITT_{800mg} included all randomly assigned patients who received a starting dose of 800 mg daily or placebo, and ITT_{All} included all randomly assigned patients, regardless of starting dosage. The Pike estimator with 95% CI of the treatment HR based on the stratified log-rank test was provided.¹³ The safety group included all randomly assigned patients who received at least one dose of study treatment (ie, safety_{600mg}, safety_{800mg}, and safety_{All}).

DFS was summarized using Kaplan-Meier survival curves. Patients who received subsequent anticancer therapy before documented recurrence or death and those who did not have a documented date of recurrence or death were censored at date of last adequate assessment (before initiation of new therapy). DFS rates and 95% CIs were summarized at yearly time points. The OS analysis of the ITT_{600mg} group used the Haybittle-Peto method,^{14,15} which assessed statistical significance, and a stratified log-rank test to compare treatment arms. A two-sided significance level of .001 was set for the latest interim OS analysis (cutoff date, October 15, 2016). Data cutoff for the final OS analysis is April 15, 2019.

RESULTS

Patients

From December 9, 2010, through September 10, 2013, 1,538 eligible patients were enrolled at 263 centers in 26 countries globally. There were 571 patients receiving pazopanib and 564 receiving placebo in the primary efficacy group (ITT_{600mg}) and 198 patients receiving pazopanib and 205 receiving placebo in the ITT_{800mg} group (Fig 1). Ten patients were randomly assigned but never treated and excluded from the safety group, including three patients in the ITT_{800mg} pazopanib group, one in the ITT_{800mg} placebo group, and six in the ITT_{600mg} placebo group. Demographic and clinical characteristics at baseline were similar in the ITT_{600mg}, ITT_{800mg}, and ITT_{All} groups and were balanced between treatment arms (Table 1).

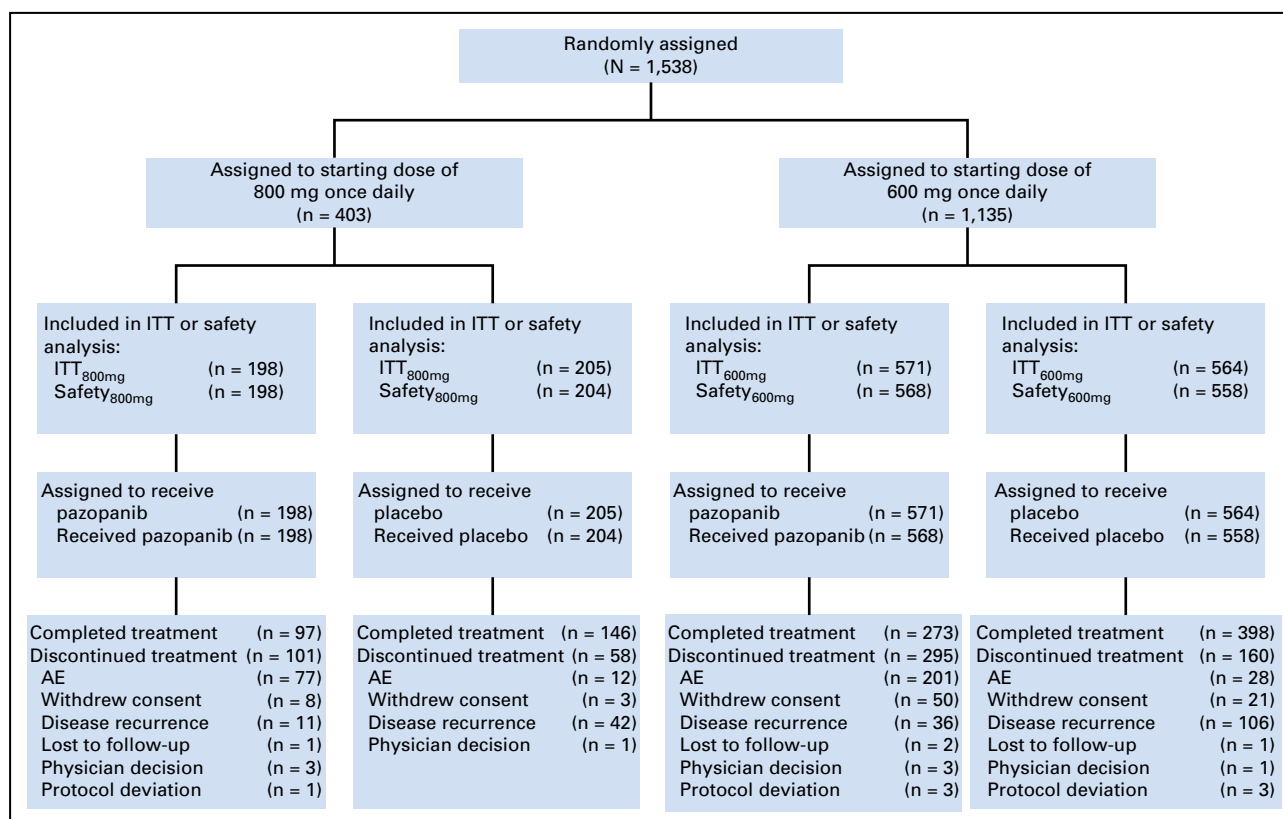


Fig 1. CONSORT diagram. AE, adverse event; ITT, intent to treat.

Efficacy

The study did not meet the primary DFS end point in the ITT_{600mg} group (HR, 0.86; 95% CI, 0.70 to 1.06; *P* = .16; Fig 2). The median duration of follow-up in the ITT_{600mg} group was 30.4 and 30.7 months for the pazopanib and placebo arms, respectively. The primary DFS analysis in the ITT_{600mg} group was not statistically significant. The results of the secondary DFS analysis demonstrated a benefit for the ITT_{800mg} (HR, 0.69; 95% CI, 0.51 to 0.94; nominal *P* = .02) and ITT_{All} (HR, 0.80; 95% CI, 0.68 to 0.95; nominal *P* = .01) groups, respectively (Figs 3A and 3B). The median duration of follow-up for both treatment arms in the ITT_{800mg} group was 47.9 months.

After 1 additional year of follow-up, the updated DFS analysis in the ITT_{600mg} group yielded an HR of 0.94 (95% CI, 0.77 to 1.14) and two-sided nominal *P* value of .51 (stratified log-rank test; Appendix Fig A1A, online only). The median DFS was not attained in either treatment arm. The DFS follow-up analysis in the ITT_{800mg} group yielded a 33.7% decrease in the relative risk of recurrence or death (HR, 0.66; 95% CI, 0.49 to 0.90; two-sided nominal *P* = .008 [stratified log-rank test]; Appendix Fig A1B). The median DFS was 54.0 months in the placebo arm and not attained in the pazopanib 800 mg arm. The proportion of patients alive and disease free decreased over time (Appendix Table A1, online only). For example, the DFS rate at 1 year was 85% (95% CI, 81% to 88%) and 76% (95% CI, 72% to 79%) for pazopanib and placebo, respectively, in the ITT_{600mg} group and 84% (95% CI, 78% to 88%) and 73% (95% CI, 66% to 78%) for pazopanib and placebo, respectively, in the ITT_{800mg} group. At 3 years, the DFS rate was

67% (95% CI, 62% to 71%) and 64% (95% CI, 60% to 68%) for pazopanib and placebo, respectively, in the ITT_{600mg} group and 66% (95% CI, 58% to 72%) and 56% (95% CI, 48% to 62%) for pazopanib and placebo, respectively, in the ITT_{800mg} group.

At the time of the DFS follow-up analysis (October 2016), the OS evaluation in the ITT_{600mg} group (based on 148 events) yielded an HR of 0.79 (95% CI, 0.57 to 1.09) and two-sided, stratified, log-rank test *P* value of .16. Survival evaluation in the ITT_{800mg} and ITT_{All} groups yielded HRs of 0.89 (95% CI, 0.54 to 1.46; *P* = .65) and 0.82 (95% CI, 0.62 to 1.07; *P* = .15), respectively (Fig 4).

Treatment Administration and Safety

The median duration of exposure was similar in the two pazopanib dose groups: 10.6 months (range, 0 to 13 months) in the safety_{600mg} and 10.2 months (range, 0 to 12 months) in the safety_{800mg} groups. The percentage of patients completing 12 months of treatment was 49% in both pazopanib dose groups and 72% and 75% in the placebo safety_{600mg} and safety_{800mg} groups, respectively. The median daily dose in the pazopanib arms was 593.7 mg (range, 129 to 800 mg) in the safety_{600mg} group and 648.4 mg (range, 178 to 800 mg) in safety_{800mg} group, whereas in the placebo arms, it was 749.2 mg (range, 200 to 800 mg) in the safety_{600mg} group and 800 mg (range, 360 to 800 mg) in the safety_{800mg} group. Twenty-one percent of patients receiving pazopanib in the safety_{600mg} group had a protocol-defined dose escalation by week 12 according to predefined safety criteria.

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	No. (%)					
	ITT _{600mg}		ITT _{800mg}		ITT _{All}	
	Pazopanib (n = 571)	Placebo (n = 564)	Pazopanib (n = 198)	Placebo (n = 205)	Pazopanib (n = 769)	Placebo (n = 769)
Age, years						
Median	58	58	56	60	58	59
Range	22-83	21-82	29-80	30-79	22-83	21-82
Sex						
Male	398 (70)	400 (71)	139 (70)	154 (75)	537 (70)	554 (72)
Female	173 (30)	164 (29)	59 (30)	51 (25)	232 (30)	215 (28)
Race						
White	471 (82)	481 (85)	168 (85)	178 (87)	639 (83)	659 (86)
Asian	71 (12)	70 (12)	28 (14)	26 (13)	99 (13)	96 (12)
Black	7 (1)	1 (< 1)	1 (< 1)	7 (1)	8 (1)	1 (< 1)
Other	4 (< 1)	2 (< 1)	0	1 (< 1)	4 (< 1)	3 (< 1)
Unknown	18 (3)	10 (2)	1 (< 1)	0	19 (2)	10 (1)
Median primary tumor size, cm	8.0	8.0	8.0	7.7	8.0	8.0
Median time since initial diagnosis, days	71.0	72	74.0	72.0	71.0	72.0
Histology						
Clear cell	530 (93)	534 (95)	181 (91)	192 (94)	528 (93)	529 (95)
Predominantly clear cell	41 (7)	30 (5)	17 (9)	13 (6)	40 (7)	29 (5)
KPS						
100	383 (67)	389 (69)	130 (66)	147 (72)	513 (67)	536 (70)
80 or 90	188 (33)	174 (31)	68 (34)	58 (28)	256 (33)	232 (30)
Unknown	0	1 (< 1)	0	0	0	1 (< 1)
Tumor stage and grade*						
pT2G3-G4N0	78 (14)	78 (14)	27 (14)	28 (14)	105 (14)	106 (14)
pT3G _{any} N0	448 (78)	440 (78)	153 (77)	162 (79)	601 (78)	602 (78)
pT4G _{any} N0 and pT _{any} G _{any} N1	45 (8)	46 (8)	18 (9)	15 (7)	63 (8)	61 (8)
Nephrectomy						
Partial	39 (7)	39 (7)	7 (4)	10 (5)	46 (6)	49 (6)
Radical	532 (93)	525 (93)	191 (96)	195 (95)	723 (94)	720 (94)
Regional lymph node status						
N0	536 (94)	534 (95)	184 (93)	194 (95)	720 (94)	728 (95)
N1	35 (6)	30 (5)	14 (7)	11 (5)	49 (6)	41 (5)
Fuhrman grade						
High (grade 3 or 4)	393 (69)	355 (63)	141 (71)	130 (63)	534 (69)	485 (63)
Low (grade 1 or 2)	178 (31)	207 (37)	57 (29)	75 (37)	235 (31)	282 (37)
Missing	0	2 (< 1)	0	0	0	2 (< 1)
Primary tumor stage						
T1	5 (< 1)	4 (< 1)	2 (1)	1 (< 1)	7 (< 1)	5 (< 1)
T2	83 (15)	83 (15)	27 (14)	30 (15)	110 (14)	113 (15)
T3	470 (82)	462 (82)	164 (83)	168 (82)	634 (82)	630 (82)
T4	13 (2)	15 (3)	5 (3)	6 (3)	18 (2)	21 (3)

Abbreviations: ITT, intent to treat; KPS, Karnofsky performance score; SSIGN, stage, size, grade, and necrosis.

*Information about necrosis was not available; thus, a modified SSIGN was used for tumor staging and grading.

Dose reductions in the pazopanib arm were performed in 289 patients (51%) in the safety_{600mg} group and 119 (60%) in the safety_{800mg} group. Discontinuations because of AEs were similar in the pazopanib safety_{600mg} and safety_{800mg} groups (35% and 39%, respectively) and in the two placebo arms (5% and 6% for safety_{600mg} and safety_{800mg}, respectively). The most common AEs leading to pazopanib discontinuation were elevations of ALT (safety_{600mg}, 16%; safety_{800mg}, 18%) and AST (safety_{600mg}, 5%; safety_{800mg}, 7%).

Overall, 98% of pazopanib-treated and 90% of placebo-treated patients in the safety_{600mg} group experienced at least one AE during therapy (Table 2). Similar AE findings during treatment were reported for patients in the safety_{800mg} group (Appendix Table A2, online only).

Two grade 5 AEs occurred during the follow-up period with placebo and four with pazopanib; three of the pazopanib deaths

occurred in the safety_{600mg} group and were considered unrelated to treatment (CNS hemorrhage, cerebral hypoxia, and renal failure), and one occurred in the safety_{800mg} group and was considered related to treatment (cardiomyopathy).

The Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (FKSI-19) questionnaire was used to gauge quality of life in the ITT_{600mg} group, and scores were similarly high in the ITT_{800mg} and ITT_{All} groups (data not shown). Pazopanib-treated patients had greater reductions from baseline in FKSI-19 total score compared with patients receiving placebo at all assessment points throughout the 12 months of treatment in the ITT_{600mg} (Appendix Fig A2, online only) and ITT_{800mg} and ITT_{All} groups (data not shown). The 1-year adjusted mean change from baseline in total FKSI-19 score with pazopanib was -4.49 for the ITT_{600mg} group compared with -0.47 with placebo (*P* < .001).

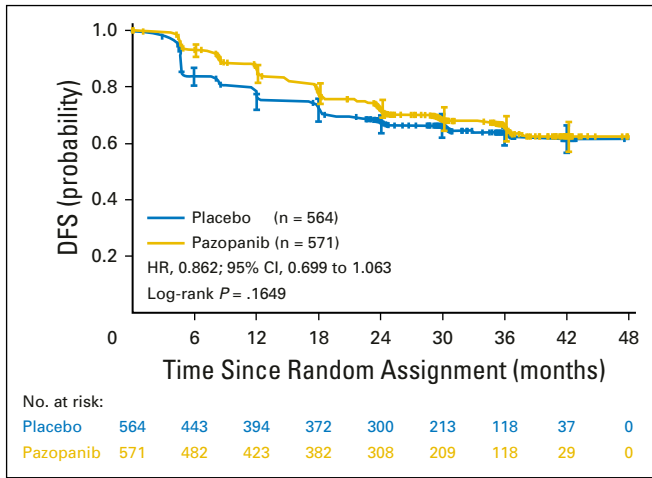


Fig 2. Disease-free survival (DFS) in the intent-to-treat pazopanib 600 mg (ITT_{600mg}) group. HR, hazard ratio.

Although significant, these changes in FKSI-19 total score did not reach the prespecified minimally important difference of 5 to be deemed clinically relevant,¹⁶ with the exception of week 8, when the mean change from baseline was -5.77 for the ITT_{600mg} group. The FKSI-19 total scores returned to baseline after treatment cessation in the pazopanib group, with no apparent difference between treatment arms during the follow-up period.

DISCUSSION

The PROTECT study did not meet the primary end point of DFS in the ITT_{600mg} group. The secondary DFS analysis in the ITT_{800mg} group showed a decrease in the relative risk of recurrence or death. However, the ITT_{800mg} group represented approximately one third of the overall study group, and DFS in this group was a secondary end point. Results of the PROTECT study showed disparate outcomes observed in the ITT_{600mg} and ITT_{800mg} groups. Considering the DFS follow-up analysis results, the difference in

treatment effect between the ITT_{600mg} and ITT_{800mg} groups could be related to the different starting dose, but it is not likely to be a result of a difference in duration of follow-up. The difference in treatment effect between the two groups might be explained by the better performance of the placebo arm in the ITT_{600mg} group compared with that in the ITT_{800mg} group, although this observation is not based on a randomized comparison. After 1 year of follow-up, the DFS rate in the placebo arm of the ITT_{600mg} group was 76% compared with 73% in the placebo arm of the ITT_{800mg} group. After 3 years of follow-up, the DFS rates in the placebo arms were 64% and 56% in the ITT_{600mg} and ITT_{800mg} groups, respectively. One factor that could explain differences in the outcomes of placebo groups includes unidentified patient demographic characteristics.

Exposure-efficacy analysis was performed among patients treated in this study.¹⁷ A correlation was observed between higher trough plasma concentration and longer DFS. A similar relationship has been reported in the metastatic setting.¹⁸ These results suggest that higher serum concentration may be associated with more clinical benefit.

With regard to OS, the results are inconclusive, because the data are not yet mature. The final data cutoff for OS analysis is planned for April 15, 2019.

The safety profile of pazopanib is consistent with that previously reported in advanced RCC studies, and the safety profile was similar for patients receiving pazopanib in the safety_{600mg} and safety_{800mg} groups. Although the intent of modifying the protocol dose of pazopanib from 800 to 600 mg was to reduce the rate of discontinuation and improve the safety profile, the proportions of patients in both cohorts had similar discontinuation rates and safety. The rate of pazopanib discontinuation because of AEs in PROTECT (35% to 39%) was higher compared with that observed in two large phase III studies in advanced or metastatic RCC (14% and 24%, respectively).^{10,12}

Approximately 21% of patients receiving pazopanib 800 mg discontinued from study drug because of transaminase elevations. In a large phase III randomized trial (COMPARZ [Comparing the Efficacy, Safety and Tolerability of Pazopanib Versus Sunitinib]),

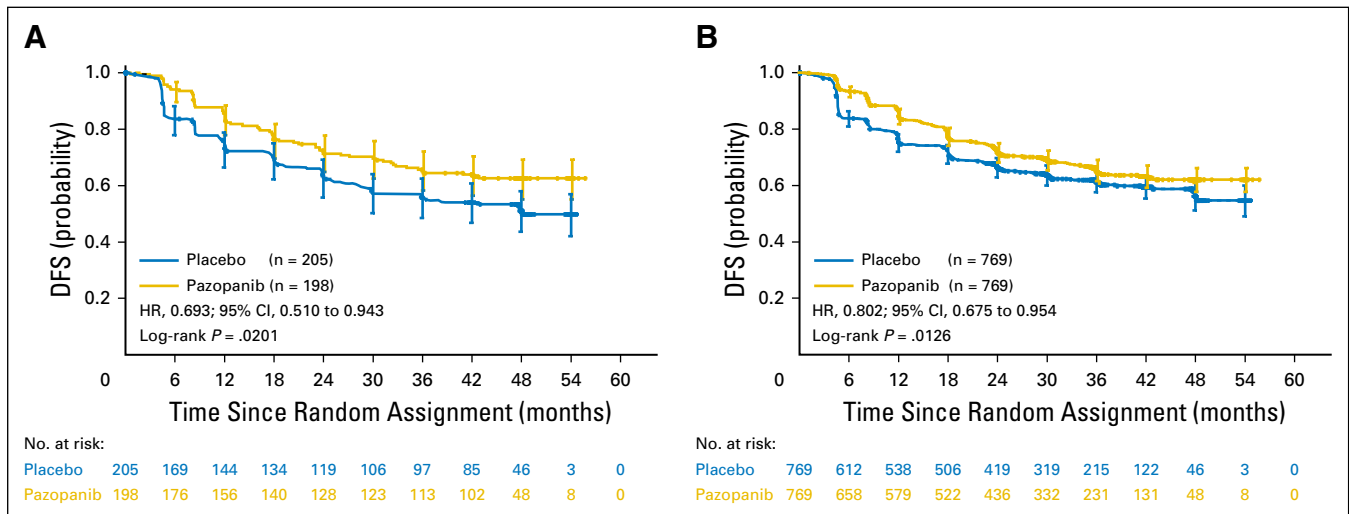


Fig 3. Disease-free survival (DFS) in the secondary cohorts of the (A) intent-to-treat pazopanib 800 mg (ITT_{800mg}) and (B) ITT_{All} groups. HR, hazard ratio.

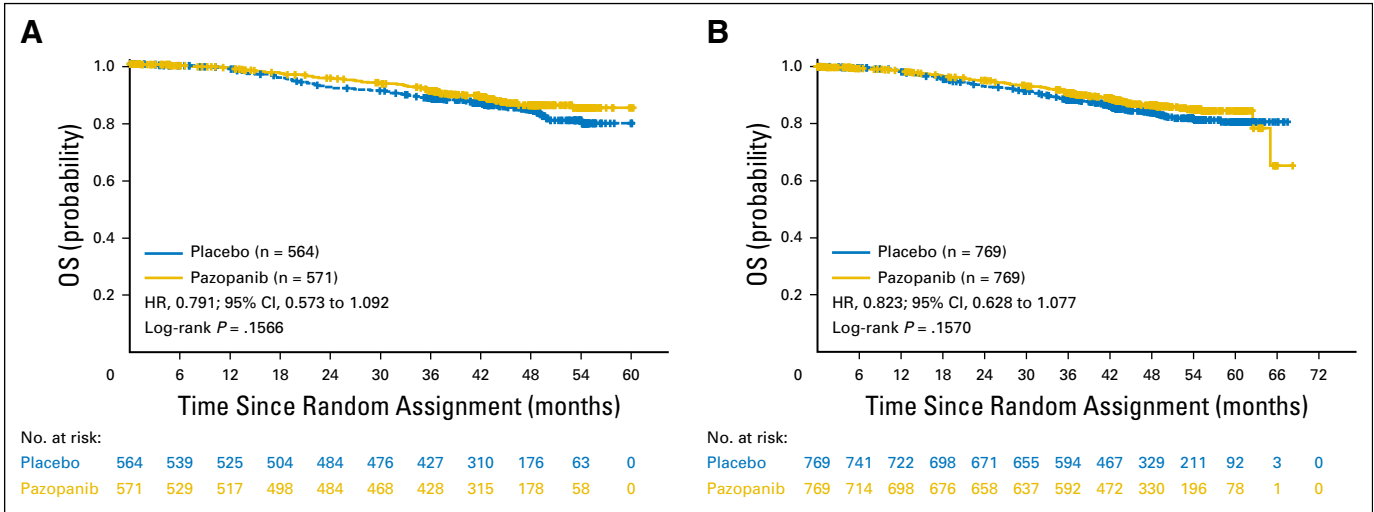


Fig 4. Interim overall survival (OS) in the (A) intent-to-treat pazopanib 600 mg (ITT_{600mg}) and (B) ITT_{All} groups. HR, hazard ratio.

6% of patients discontinued pazopanib for abnormalities in liver function tests.¹² This difference may be explained by more stringent criteria defined for the management of liver enzyme elevation in PROTECT. Overall, ALT increases were reversible and manageable with pazopanib dose interruptions or reductions provided in the protocol guidelines. The evaluation of outcomes for patients with ALT > 3× the upper limit of normal showed that 99% of all those receiving pazopanib recovered to grade ≤ 1.

Health-related quality of life deteriorated during treatment with pazopanib, showing a slight trend toward improvement over time; quality of life was promptly restored back to baseline levels after treatment.

The efficacy results of PROTECT follow conflicting results from the two other large adjuvant trials in RCC. The ASSURE trial (comparing adjuvant sorafenib and sunitinib v placebo) failed to meet its primary end point,⁷ whereas the S-TRAC trial (comparing

Table 2. AEs During Therapy by Maximum Grade (pazopanib, ≥ 10% in any grade) in Safety_{600mg} Group

AE	No. (%)			
	Pazopanib (n = 568)		Placebo (n = 558)	
	All Grades	Grade 3 to 4	All Grades	Grade 3 to 4
Any AE	558 (98)	338 (60)	501 (90)	119 (21)
Diarrhea	362 (64)	38 (7)	139 (25)	4 (< 1)
Hypertension	295 (52)	141 (25)	107 (19)	37 (7)
Hair color changes	232 (41)	0	28 (5)	0
Nausea	226 (40)	2 (< 1)	89 (16)	0
Fatigue	222 (39)	13 (2)	144 (26)	4 (< 1)
Increased ALT	196 (35)	91 (16)	28 (5)	5 (< 1)
Dysgeusia	170 (30)	3 (< 1)	15 (3)	0
Increased AST	141 (25)	34 (6)	22 (4)	1 (< 1)
Headache	139 (24)	2 (< 1)	78 (14)	1 (< 1)
Decreased appetite	113 (20)	2 (< 1)	23 (4)	0
Palmar-plantar erythrodysesthesia	102 (18)	11 (2)	24 (4)	0
Vomiting	96 (17)	1 (< 1)	21 (4)	1 (< 1)
Abdominal pain	85 (15)	4 (< 1)	45 (8)	1 (< 1)
Asthenia	79 (14)	5 (< 1)	53 (9)	2 (< 1)
Alopecia	64 (11)	0	20 (4)	0
Rash	63 (11)	1 (< 1)	36 (6)	0
Abdominal pain upper	58 (10)	4 (< 1)	18 (3)	0
Dysphoria	55 (10)	0	10 (2)	1 (< 1)
Hypothyroidism	55 (10)	0	4 (< 1)	0
Stomatitis	55 (10)	2 (< 1)	22 (4)	0
Back pain	52 (9)	1 (< 1)	77 (14)	3 (< 1)
Arthralgia	43 (8)	0	67 (12)	0

NOTE. During therapy is defined as the time from first dose of study treatment to the date of last dose of study treatment plus 28 days. Listed are AEs reported in ≥ 10% of patients in either arm.
 Abbreviation: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

adjuvant sunitinib v placebo) met its primary end point.⁸ These three trials enrolled generally similar patient populations with intermediate to high risk of relapse. However, the stratification of the risk of relapse was performed differently in these studies; moreover, some differences existed between the respective study populations as well as the drug administered. For example, in PROTECT, the population consisted of patients with intermediate or high risk defined by the SSIGN scoring algorithm,¹⁹ whereas the UISS (University of California-Los Angeles Integrated Staging System) risk stratification system²⁰ was used in S-TRAC and ASSURE. All patients in S-TRAC presented with stage T3 or T4 disease, whereas in PROTECT, T3 or T4 represented 84% of patients. The ASSURE trial enrolled a broader patient population, including patients with stage T1b high-grade disease (15%), and the proportion of patients with stage T3 or T4 disease was approximately 65%. ASSURE was the only trial that enrolled patients with non-clear cell histology; this subgroup comprised 20% of the patient population. Although the patient populations of these studies differed somewhat, they all enrolled patients with a high risk of relapse.¹³

Findings from PROTECT demonstrated differences in outcome between the 600- and 800-mg starting dose groups; however, the study did not meet its primary DFS end point. The results of the primary analysis of DFS with pazopanib 600 mg showed no benefit over placebo in the adjuvant setting. The safety profile of pazopanib was consistent with prior experience.

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AUTHOR CONTRIBUTIONS

Conception and design: Robert J. Motzer, Naomi B. Haas, Brian I. Rini, Ho Yeong Lim, Paul Russo, Cora N. Sternberg

Provision of study materials or patients: Robert J. Motzer, Naomi B. Haas, Frede Donskov, Marine Gross-Goupil, Jae Lyun Lee, Bohuslav Melichar, Brian I. Rini, Toni K. Choueiri, Lori A. Wood, Paul Russo

Collection and assembly of data: Robert J. Motzer, Frede Donskov, Marine Gross-Goupil, Sergei Varlamov, Evgeny Kopyltsov, Jae Lyun Lee, Bohuslav Melichar, Brian I. Rini, Toni K. Choueiri, Milada Zemanova, Lori A. Wood, M. Neil Reaume, Arnulf Stenzl, Simon Chowdhury, Ray McDermott, Agnieszka Michael, Marlene J. Carrasco-Alfonso, Paul Russo, Cora N. Sternberg

Data analysis and interpretation: Robert J. Motzer, Naomi B. Haas, Frede Donskov, Jae Lyun Lee, Bohuslav Melichar, Brian I. Rini, Toni K. Choueiri, Simon Chowdhury, Ray McDermott, Weichao Bao, Marlene J. Carrasco-Alfonso, Paola Aimone, Maurizio Voi, Christian Doehn, Paul Russo, Cora N. Sternberg

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

observation of each patient: II. Analysis and examples. *Br J Cancer* 35:1-39, 1977

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Affiliations

Robert J. Motzer and **Paul Russo**, Memorial Sloan Kettering Cancer Center, New York, NY; **Naomi B. Haas**, University of Pennsylvania, Philadelphia, PA; **Frede Donskov**, Aarhus University Hospital, Aarhus, Denmark; **Marine Gross-Goupil**, Bordeaux University Hospital, Bordeaux, France; **Sergei Varlamov**, Altai Regional Cancer Center, Barnaul; **Evgeny Kopyltsov**, State Institution of Healthcare Regional Clinical Oncology Dispensary, Omsk, Russia; **Jae Lyun Lee**, University of Ulsan College of Medicine; **Ho Yeong Lim**, Sungkyunkwan University, Seoul, Republic of Korea; **Bohuslav Melichar**, Palacky University Medical School and Teaching Hospital,

Olomouc; **Milada Zemanova**, Charles University and General University Hospital, Prague, Czech Republic; **Brian I. Rini**, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; **Toni K. Choueiri**, Dana-Farber Cancer Institute, Boston, MA; **Lori A. Wood**, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, Nova Scotia; **M. Neil Reaume**, Ottawa Hospital Cancer Centre, Ottawa, Ontario, Canada; **Arnulf Stenzl**, University Hospital Tübingen, Tübingen; **Christian Doehn**, University of Lübeck Medical School and Urologikum Lübeck, Lübeck, Germany; **Simon Chowdhury**, Guy's and St Thomas' National Health Service Foundation/St Thomas' Hospital, London; **Ray McDermott**, Tallaght University Hospital and Cancer Trials Ireland, Dublin; **Agnieszka Michael**, University of Surrey, Guildford, United Kingdom; **Weichao Bao**, **Marlene J. Carrasco-Alfonso**, and **Maurizio Voi**, Novartis Oncology, East Hanover, NJ; **Paola Aimone**, Novartis Pharma AG, Basel, Switzerland; and **Cora N. Sternberg**, San Camillo Forlanini Hospital, Rome, Italy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma

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Robert J. Motzer

Consulting or Advisory Role: Pfizer, Novartis, Eisai, Exelixis

Research Funding: Pfizer (Inst), GlaxoSmithKline (Inst), Bristol-Myers Squibb (Inst), Eisai (Inst), Novartis (Inst), Genentech (Inst)

Naomi B. Haas

Consulting or Advisory Role: Cerulean Pharma, Exelixis, Pfizer, Novartis

Expert Testimony: Eli Lilly (I)

Stock or Other Ownership: Tetralogic

Frede Donskov

Research Funding: GlaxoSmithKline (Inst), Novartis (Inst), Pfizer (Inst)

Travel, Accommodations, Expenses: Exelixis

Marine Gross-Goupil

Honoraria: Pfizer, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Ipsen

Consulting or Advisory Role: Pfizer, Novartis, GlaxoSmithKline, Bristol-Myers Squibb

Speakers' Bureau: Novartis

Research Funding: GlaxoSmithKline (Inst), Pfizer (Inst), Ipsen (Inst), Roche (Inst), Bristol-Myers Squibb (Inst), Novartis (Inst), Astellas (Inst), Janssen (Inst)

Travel, Accommodations, Expenses: Amgen, Merck Sharp & Dohme, Pfizer, Novartis, Roche, Bristol-Myers Squibb

Sergei Varlamov

No relationship to disclose

Evgeny Kopyltsov

No relationship to disclose

Jae Lyun Lee

Honoraria: Pfizer, Astellas Pharma, Novartis

Consulting or Advisory Role: Astellas Pharma, AstraZeneca, Eisai

Research Funding: Pfizer, Janssen, Novartis, Exelixis, Bayer

Bohuslav Melichar

Honoraria: Roche Pharma AG, Novartis, Ipsen, Bristol-Myers Squibb, Astellas Pharma, Pfizer, Eli Lilly, Janssen-Cilag, Merck, Merck Sharp & Dohme, Angelini Pharma, Bayer HealthCare Pharmaceuticals

Consulting or Advisory Role: Roche Pharma AG, Novartis, Bristol-Myers Squibb, Astellas Pharma, Bayer HealthCare Pharmaceuticals, Pfizer, Merck, Merck Sharp & Dohme

Travel, Accommodations, Expenses: Novartis, Roche, Bristol-Myers Squibb, Merck

Brian I. Rini

Consulting or Advisory Role: Pfizer, Roche, Bristol-Myers Squibb, Acceleron, Novartis, GlaxoSmithKline

Research Funding: Pfizer (Inst), Genentech (Inst), Bristol-Myers Squibb (Inst), Acceleron (Inst), Immatics (Inst), Peloton (Inst)

Travel, Accommodations, Expenses: Pfizer

Toni K. Choueiri

Honoraria: National Comprehensive Cancer Network, UpToDate

Consulting or Advisory Role: Pfizer, Bayer HealthCare Pharmaceuticals, Novartis, Merck, Bristol-Myers Squibb, Genentech, Eisai, Foundation Medicine, Cerulean Pharma, AstraZeneca, Peloton Therapeutics, Exelixis, Prometheus, Alligent, GlaxoSmithKline, Roche

Research Funding: Pfizer (Inst), Novartis (Inst), Merck (Inst), Exelixis (Inst), TRACON Pharma (Inst), GlaxoSmithKline (Inst), Bristol-Myers Squibb (Inst), AstraZeneca (Inst), Peloton Therapeutics (Inst), Genentech (Inst), Celldex (Inst), Agensys (Inst), Roche (Inst)

Milada Zemanova

Consulting or Advisory Role: Novartis

Honoraria: Eli Lilly

Travel, Accommodations, Expenses: Merck Sharp & Dohme, Boehringer Ingelheim

Lori A. Wood

Research Funding: Bristol-Myers Squibb (Inst), Merck (Inst), Novartis (Inst), Pfizer (Inst), Roche (Inst), AstraZeneca (Inst),

M. Neil Reaume

Consulting or Advisory Role: Novartis, Sanofi, Pfizer, Janssen, Roche Canada

Arnulf Stenzl

Consulting or Advisory Role: Ipsen, Janssen, Amgen, Roche Pharma AG, Bayer HealthCare Pharmaceuticals, Takeda Pharmaceuticals, CureVac, Intuitive Surgical SARL, Bristol-Myers Squibb, Alere

Honoraria: Ipsen Pharma, Janssen, Alere

Speakers' Bureau: Ipsen, Janssen, Alere, General Electric, Amgen, CureVac, Erbe, Novartis, Karl Storz

Research Funding: Novartis (Inst), Ipsen (Inst), Bayer AG (Inst), CureVac (Inst), Immatics Biotechnologies (Inst), Janssen (Inst), Convance (Inst), Johnson & Johnson, Amgen

Travel, Accommodations, Expenses: Alere, Amgen, CureVac, Ipsen, Novartis, Janssen, Erbe, Karl Storz, Astellas Pharma, Roche

Simon Chowdhury

Honoraria: GlaxoSmithKline, Novartis

Consulting or Advisory Role: GlaxoSmithKline, Novartis, Pfizer, Johnson & Johnson, Astellas, Bayer

Research Funding: Sanofi

Speakers' Bureau: GlaxoSmithKline, Johnson & Johnson, Astellas, Bayer
Travel, Accommodations, Expenses: GlaxoSmithKline, Novartis, Johnson & Johnson, Astellas, Bayer

Ho Yeong Lim

No relationship to disclose

Ray McDermott

Consulting or Advisory Role: Clovis Oncology, Pfizer, Amgen, Bristol-Myers Squibb

Honoraria: Bristol-Myers Squibb, Sanofi, Janssen, Celgene, Pfizer, Novartis, Astellas, Bayer

Research Funding: Pfizer, Janssen, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb, Merck, Sharp & Dohme, Astellas, Sanofi

Travel, Accommodations, Expenses: Pfizer, Celgene

Adjuvant Pazopanib in Renal Cell Carcinoma After Nephrectomy

Agnieszka Michael

Honoraria: Pfizer, Bristol-Myers Squibb
Travel, Accommodations, Expenses: Ipsen

Weichao Bao

Employment: Novartis
Stock or Other Ownership: Novartis

Marlene J. Carrasco-Alfonso

Employment: Novartis
Stock or Other Ownership: Novartis, Kite Pharma (I), Juno Therapeutics (I), Bluebird Bio (I), Bellicum Pharmaceuticals (I), Cellectis (I), Lion Biotechnologies (I), Adaptimmune (I), Intellia Therapeutics (I), Editas Medicine (I)

Paola Aimone

Employment: Novartis Pharma AG
Stock or Other Ownership: Novartis Pharma AG
Travel, Accommodations, Expenses: Novartis Pharma AG

Maurizio Voi

Employment: Novartis
Stock or Other Ownership: Novartis, Pfizer, Bristol-Myers Squibb
Patents, Royalties, Other Intellectual Property: Bristol-Myers Squibb

Christian Doehn

Stock or Other Ownership: AstraZeneca, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb, Fresenius
Honoraria: Amgen, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Pfizer, Roche
Consulting or Advisory Role: Amgen, Bristol-Myers Squibb, Novartis, Pfizer, Bayer HealthCare Pharmaceuticals, Eisai, GlaxoSmithKline, Ipsen, Roche
Travel, Accommodations, Expenses: Amgen, Bristol-Myers Squibb, Novartis, Pfizer, Roche

Paul Russo

No relationship to disclose

Cora N. Sternberg

Honoraria: Pfizer, Bristol-Myers Squibb, Novartis, Janssen, Bayer HealthCare Pharmaceuticals, Astellas Pharma, Sanofi, Eisai, Ipsen, GlaxoSmithKline, Merck Sharp & Dohme, Eli Lilly
Research Funding: Exelixis (Inst)

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Appendix

Exclusion Criteria

Patients were excluded if they had locally recurrent or bilateral renal cell carcinoma (RCC) or history of another malignancy, unless they had been disease free for 5 years or had a history of completely resected nonmelanomatous skin carcinoma or successfully treated in situ carcinoma; had clinically significant GI abnormalities that may increase the risk for GI bleeding or affect absorption of investigational product; active diarrhea of any grade; had history of HIV infection, chronic active hepatitis, or uncontrolled infection; had history of cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery bypass graft surgery, or symptomatic peripheral arterial vascular disease within the past 6 months; had history of class III/IV congestive heart failure defined per the New York Heart Association classification; had history of cerebrovascular accident, including transient ischemic attack, pulmonary embolism, or untreated deep venous thrombosis within the past 6 months; had corrected QT interval > 480 msec; had poorly controlled hypertension (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic blood pressure); had evidence of active bleeding or bleeding diathesis; had any serious and/or unstable preexisting medical, psychiatric, or other condition that could interfere with patient safety, provision of informed consent, or compliance with study procedures; were unable or unwilling to discontinue use of various prohibited medications for at least 14 days or five half-lives of a drug (whichever was longer) before the first dose of study treatment and for the duration of the study; were receiving concurrent therapy to treat cancer, including treatment with an investigational agent, or concurrently participating in another clinical trial involving an anticancer investigational drug; had received any investigational drug within 30 days or five half-lives (whichever was longer) before the first dose of study treatment; had a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib or excipients that in the opinion of the investigator contradicted their participation; or had used or were using systemic antivasculature endothelial growth factor inhibitors or cytokines (eg, interferon, interleukin-2).

Disease, Safety, and Quality-of-Life Assessments

Disease assessments were performed using computed tomography (CT) or magnetic resonance imaging (MRI) at baseline; weeks 20, 36, and 52 during year 1; every 6 months during years 2 to 5; and yearly thereafter. Baseline imaging was performed a minimum of 4 weeks after nephrectomy and at least 2 weeks before random assignment. Baseline disease-free status was assessed locally and confirmed by central review. Local RCC recurrence or distal metastasis was diagnosed only when the clinical, imaging, or pathologic findings met predefined criteria consistent with recurrence or metastasis. Safety was assessed during clinic visits and as clinically indicated. After established disease recurrence, patients were observed for survival every 6 months until death, study completion, or early study termination.

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). RCC symptoms were assessed using the Functional Assessment of Cancer Therapy Kidney Symptom Index 19 (FKSI-19). Quality-of-life (QoL) changes from baseline were evaluated for pazopanib and placebo during the treatment period, disease-free survival (DFS) period, and study period after disease recurrence. Plasma samples for clinical pharmacology assessments were also collected.

Assessment of Recurrence, Safety, and Compliance

Assessment of the primary end point of DFS was based on evaluation of imaging scans. The preferred imaging assessment method for the chest, abdomen, and pelvis was CT with intravenous contrast. Clinical assessments included medical history and physical examination for possible palpable lesions (eg, lymph nodes) or visual lesions and for evaluation of other signs or symptoms that may be suggestive of local disease or metastatic lesions. Pathology assessments included cytology or histology by needle aspiration or biopsy.

Required baseline imaging consisted of CT/MRI of chest, abdomen, and pelvis. Baseline imaging was performed after a minimum of 4 weeks after nephrectomy. On the day of random assignment (day 1) before dosing, patients completed the QoL questionnaires and underwent a physical examination. New abnormal conditions or concurrent medications were to be documented, and blood samples for biomarker and pharmacogenetic assessments were drawn. CT or MRI of the chest, abdomen, and

pelvis was performed at weeks 20, 36, and 52 (\pm 14 days) during the first year of treatment; every 6 months (\pm 21 days) from the start of year 2 through year 5; and every 12 months (\pm 21 days) from the start of year 6 onward. Brain and bone scans were to be performed as clinically indicated.

Once a patient presented with established disease recurrence, he or she was observed using the telephone every 6 months for survival until death, study completion, or early termination of study by the independent data monitoring committee.

Safety assessments included physical examination, clinical laboratory tests (including clinical chemistry, hematology, coagulation, thyroid function, and urinalysis), ECG, Karnofsky performance score, vital signs, evaluation of concomitant medications, and pregnancy test (if applicable). Screening safety assessments were not performed before recovery of patients from nephrectomy and/or its complications to grade \leq 1 severity. Screening safety assessments were also used as baseline for patients who were eligible for the study, and the assessments were only valid if they were within 4 weeks (28 days) of random assignment. If treatment discontinuation occurred in between scheduled visits, safety assessments (with exception of ECG and thyroid function test) were performed if the previous assessments were reported $>$ 4 weeks previously. ECG and thyroid function tests were performed if the previous assessments were $>$ 12 weeks old.

The investigator or site staff was responsible for detecting, documenting, and reporting events that met the criteria for AEs. Information about the AEs volunteered by the patient, discovered by investigator questioning, or detected by other means was collected from the start of study treatment until follow-up. The following information on AEs was obtained: duration (start and stop dates), severity (mild, moderate, or severe), causality (reasonable possibility [yes or no]), and actions taken and outcome.

Abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiologic scans, vital signs measurements), including those that worsened from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator were recorded as AEs. Clinically significant safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition, were not reported as AEs. All AEs were monitored until resolution or recovery to the baseline severity. Death resulting from disease during study was recorded.

Compliance with study treatment was confirmed by the sites through querying the patients during the site visits and documented. The number of study treatment tablets dispensed to and taken by each patient was recorded and reconciled with the study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions, were recorded.

Source of Drug, Dose Adjustments, and Discontinuations Because of AEs

After completion of required screening/baseline assessments, eligible patients were registered in the GlaxoSmithKline Registration and Medication Ordering System (RAMOS) by the investigator or authorized site staff for stratification and random assignment. Patient identification and the following information for stratification were entered into the RAMOS system to obtain blinded study treatment assignment: nephrectomy procedure (partial ν radical [including total nephrectomy]) and TNM stage and tumor grade groups, as described in Patients and Methods.

Patients were centrally assigned to the pazopanib or placebo arm at a one-to-one ratio. Treatment assignment remained blinded until a patient was confirmed to have disease recurrence or development of distal metastasis or until the study achieved the primary end point of DFS.

The maximum allowable pazopanib dose was 800 mg daily, and the minimum allowable dose was 400 mg daily. As a general rule, if dose reduction of study treatment was necessary, the dose was reduced stepwise by 200 mg at each step, and the patient was monitored for approximately 10 to 14 days at each dose level. If the investigator believed that further reduction to 200 mg daily was required, the investigator contacted the sponsor's study physician to determine appropriateness.

After abatement of toxicity with modified dose and management of adverse effects, dose re-escalation back to the pre-event dose was attempted. For patients whose treatment was interrupted for liver events, study treatment was rechallenged at a dose of 400 mg daily. If a patient's study treatment was interrupted for $>$ 21 days, the investigator was contacted the study physician to review the patient's condition to resume treatment.

Patients who were assigned to study treatment at the dose level of 600 mg daily did not receive a higher dose for the first 8 to 12 weeks of treatment. Starting at the week-8 visit, the investigator determined whether to escalate the dose to 800 mg daily or maintain the dose at 600 mg daily based on a patient's safety and tolerability profile since the first dose and in accordance with the following dose-escalation criteria: no or only grade 1 treatment-related AEs, no ongoing grade 2 treatment-related AEs (could have had grade 2 treatment-related AEs that recovered to grade \leq 1), no grade 3 or 4 treatment-related AEs, and ALT \leq upper limit of normal.

AEs of hair color change and alopecia were excluded when applying these criteria for dose escalation. For patients with multiple ongoing treatment-related grade 1 AEs (eg, > three AEs), dose escalation to the 800-mg dose level was based on the investigator's clinical judgment. If a patient could not be dose escalated at week 8 because of ongoing treatment-related grade 2 AEs, the patient was re-evaluated at week 12 for the possibility of dose escalation to the 800-mg dose level. If the dose could not be escalated to 800 mg daily between weeks 8 and 12, the patient maintained a maximum 600-mg dose for the rest of the treatment period unless subsequent dose reduction was necessary because of an AE.

If an AE was considered unlikely to be related to study treatment per the investigator's clinical judgment, these dose modification rules did not apply.

Health Outcome Assessments

RCC symptoms affecting health-related QoL were assessed using the FKSI-19. This assessment was used to evaluate changes from baseline health-related QoL for pazopanib compared with placebo during the following study periods: 12 months of treatment, DFS, and after disease recurrence.

The FKSI-19 is a disease-specific assessment that measures disease- and treatment-related symptoms specifically in patients with renal cancer (Rosenbloom SK, et al: *J Clin Oncol* 25, 2007 [suppl; abstr 6524]; Rosenbloom S, et al: *Res Hum Cap Dev* 16:53-66, 2008; Rao D, et al: *J Pain Symptom Manage* 38:291-298, 2009). It includes patient self-reports on experience of symptoms in the past 7 days (eg, lack of energy, pain, bone pain, shortness of breath, fatigue, blood in urine).

These questionnaires were administered following the same schedule as the CT scans (ie, at baseline [day 1 predose]; weeks 8, 20, 36, and 52; every 6 months during years 2 to 5; and once every year starting at year 6). In addition, QoL questionnaires were completed by patients via mail approximately 3 months after documented disease recurrence.

Adjuvant Pazopanib in Renal Cell Carcinoma After Nephrectomy

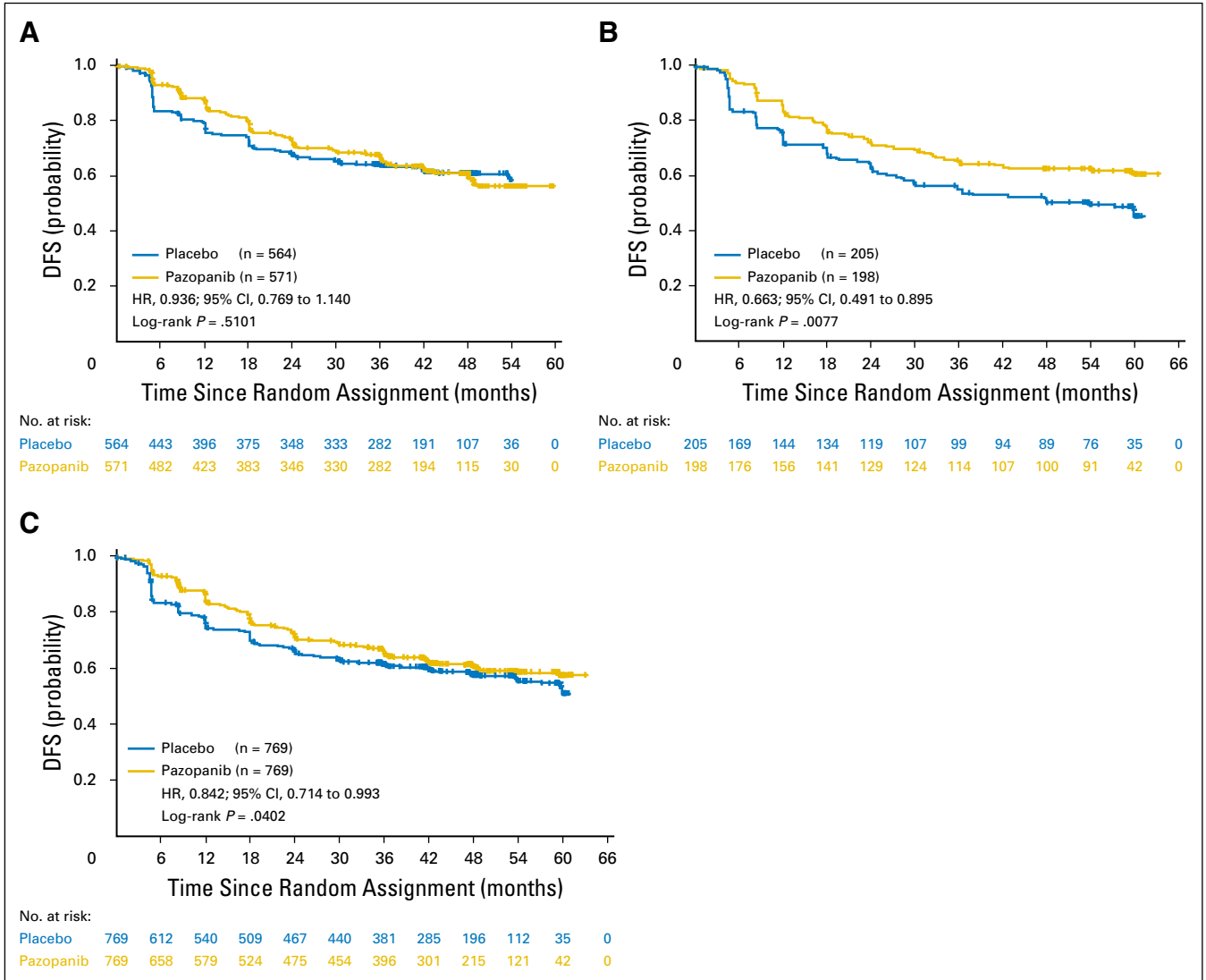


Fig A1. Disease-free survival (DFS) in the (A) intent-to-treat pazopanib 600 mg (ITT_{600mg}), (B) ITT_{800mg}, and (C) ITT_{All} groups (follow-up analysis of DFS on October 15, 2016).

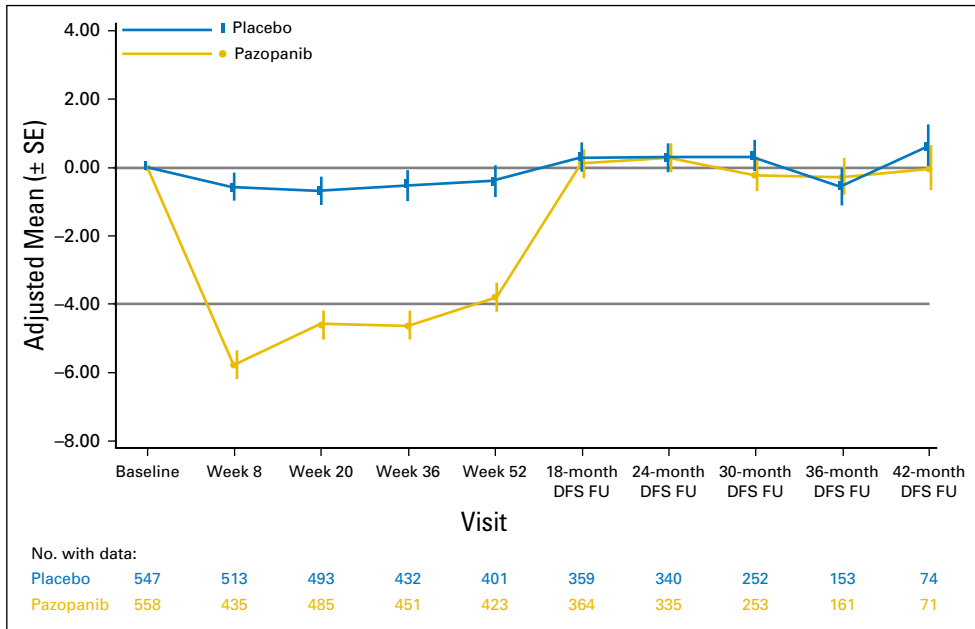


Fig A2. Health-related quality-of-life outcomes in the intent-to-treat pazopanib 600 mg group assessed using the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Kidney Symptom Index 19 questionnaire total score. DFS, disease-free survival; FU, follow-up.

Table A1. DFS at Annual Intervals

DFS Analysis	DFS (%) (95% CI)					
	ITT _{600mg}		ITT _{800mg}		ITT _{All}	
	Pazopanib (n = 571)	Placebo (n = 564)	Pazopanib (n = 198)	Placebo (n = 205)	Pazopanib (n = 769)	Placebo (n = 769)
Follow-up	0.936		0.663		0.842	
HR	0.769 to 1.140		0.491 to 0.895		0.714 to 0.993	
95% CI	85 (81 to 88)	76 (72 to 79)	84 (78 to 88)	73 (66 to 78)	85 (82 to 87)	75 (72 to 78)
1 year	71 (67 to 75)	68 (64 to 72)	72 (65 to 78)	62 (55 to 69)	72 (68 to 75)	66 (63 to 70)
2 years	67 (62 to 71)	64 (60 to 68)	66 (58 to 72)	56 (48 to 62)	66 (63 to 70)	62 (58 to 65)
3 years	61 (56 to 65)	61 (56 to 65)	63 (55 to 69)	51 (44 to 58)	62 (58 to 65)	58 (54 to 62)
4 years	NA	NA	61 (53 to 68)	48 (40 to 55)	58 (53 to 62)	54 (48 to 58)
5 years						

Abbreviations: DFS, disease-free survival; HR, hazard ratio; ITT, intent to treat; NA, not available.

Adjuvant Pazopanib in Renal Cell Carcinoma After Nephrectomy

Table A2. AEs During Therapy by Maximum Grade (pazopanib, > 10% in any grade) in Safety_{800mg} Group

AE	No. (%)			
	Pazopanib (n = 198)		Placebo (n = 204)	
	All Grades	Grade 3 to 4	All Grades	Grade 3 to 4
Any AE	197 (> 99)	131 (66)	174 (85)	42 (21)
Diarrhea	129 (65)	14 (7)	48 (24)	3 (1)
Hypertension	109 (55)	56 (28)	29 (14)	9 (4)
Hair color changes	90 (45)	1 (< 1)	9 (4)	0
Nausea	89 (45)	2 (1)	28 (14)	0
Fatigue	74 (37)	4 (2)	53 (26)	1 (< 1)
Increased ALT	65 (33)	29 (15)	11 (5)	0
Headache	58 (29)	6 (3)	35 (17)	1 (< 1)
Increased AST	48 (24)	12 (6)	5 (2)	0
Dysgeusia	43 (22)	1 (< 1)	5 (2)	0
Decreased appetite	42 (21)	1 (< 1)	11 (5)	0
Palmar-plantar erythrodysesthesia	42 (21)	8 (4)	8 (4)	0
Vomiting	37 (19)	2 (1)	9 (4)	2 (< 1)
Abdominal pain	28 (14)	4 (2)	24 (12)	0
Back pain	28 (14)	2 (1)	15 (7)	1 (< 1)
Alopecia	26 (13)	1 (< 1)	6 (3)	0
Dizziness	26 (13)	0	17 (8)	0
Asthenia	24 (12)	3 (2)	12 (6)	0
Hypothyroidism	24 (12)	0	2 (< 1)	0
Rash	24 (12)	0	14 (7)	0
Stomatitis	23 (12)	0	11 (5)	0
Mucosal inflammation	21 (11)	2 (1)	4 (2)	0
Arthralgia	20 (10)	1 (< 1)	13 (6)	0
Pain in extremity	20 (10)	4 (2)	12 (6)	0

NOTE. During therapy is defined as the time from first dose of study treatment to the date of last dose of study treatment plus 28 days. Listed are AEs reported in > 10% of patients in either arm.

Abbreviation: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.