original reports

Adjuvant Sorafenib for Renal Cell Carcinoma at Intermediate or High Risk of Relapse: Results From the SORCE Randomized Phase III Intergroup Trial

Tim Eisen, MB BChir, PhD[1]; Eleni Frangou, MSc (Res)[2]; Bhavna Oza, MBBS[2]; Alastair W.S. Ritchie, MD[2]; Benjamin Smith, BSc[2]; Rick Kaplan, MD[2]; Ian D. Davis, MBBS, PhD[3]; Martin R. Stockler, MBBS, MSc[4]; Laurence Albiges, MD, PhD[5]; Bernard Escudier, MD[5]; James Larkin, PhD[6]; Axel Bex, MD, PhD[7,8]; Steven Joniau, MD, PhD[9]; Barry Hancock, MD[10]; Gregers G. Hermann, MD, DMSc[11]; Joaquim Bellmunt, MD, PhD[12]; Elizabeth Hodgkinson, BPharm, MSc[13]; Grant D. Stewart, MBChB[14]; Jim Barber, DM[15]; Janet Brown, MD[16,17]; Rhona McMenemin, MSc[18]; Paul Nathan, MBBS, MD[19]; Lisa M. Pickering, PhD[6]; Mahesh K.B. Parmar, DPhil[2]; and Angela Meade, DPhil[2]

abstract

PURPOSE SORCE is an international, randomized, double-blind, three-arm trial of sorafenib after surgical excision of primary renal cell carcinoma (RCC) found to be at intermediate or high risk of recurrence.

PATIENTS AND METHODS We randomly assigned participants (2:3:3) to 3 years of placebo (arm A), 1 year of sorafenib followed by 2 years of placebo (arm B), or 3 years of sorafenib (arm C). The initial sorafenib dose was 400 mg twice per day orally, amended to 400 mg daily. The primary outcome analysis, which was revised as a result of external results, was investigator-reported disease-free survival (DFS) comparing 3 years of sorafenib versus placebo.

RESULTS Between July 2007 and April 2013, we randomly assigned 1,711 participants (430, 642, and 639 participants in arms A, B, and C, respectively). Median age was 58 years, 71% of patients were men, 84% had clear cell histology, 53% were at intermediate risk of recurrence, and 47% were at high risk of recurrence. We observed no differences in DFS or overall survival in all randomly assigned patients, patients with high risk of recurrence, or patients with clear cell RCC only. Median DFS was not reached for 3 years of sorafenib or for placebo (hazard ratio, 1.01; 95% CI, 0.83 to 1.23; $P = .95$). We observed nonproportional hazards; the restricted mean survival time (RMST) was 6.81 years for 3 years of sorafenib and 6.82 years for placebo (RMST difference, 0.01 year; 95% CI, −0.49 to 0.48 year; $P = .99$). Despite offering treatment adaptations, more than half of participants stopped treatment by 12 months. Grade 3 hand-foot skin reaction was reported in 24% of participants on sorafenib.

CONCLUSION Sorafenib should not be used as adjuvant therapy for RCC. Active surveillance remains the standard of care for patients at intermediate or high risk of recurrence after nephrectomy and is the appropriate control of our current international adjuvant RCC trial, RAMPART.

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ASSOCIATED CONTENT

Appendix

Protocol

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

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INTRODUCTION

In 2018, > 400,000 new renal cell carcinomas (RCCs) were diagnosed, and 175,098 deaths were attributed to RCC worldwide.[1] Two thirds of patients with RCC present with disease confined to the kidney, which is potentially curable by surgery alone. Scoring systems, such as the Leibovich score, use clinical factors to categorize patients according to their risk of relapse or death. Patients with intermediate- or high-risk RCC after surgical resection are at significant risk of relapse and death. The 5-year relapse rate for these patients is 30%-40%; 5-year survival has been reported at 74.8%, which declines steeply to 16% once patients develop metastatic disease.[2]

Effective treatments to reduce the risk of recurrence or cancer death in patients with locoregional RCC remain an unmet clinical need. Adjuvant strategies in RCC, including cytokines, radiotherapy, and hormone therapy, have been explored with no success.[3] Oral tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor (VEGF) receptor, including sunitinib, sorafenib, and pazopanib, are effective in metastatic RCC, which supported their evaluation in the adjuvant setting and our decision to investigate the use of the multitargeted TKI sorafenib in the SORCE trial.[4-6]

Four randomized controlled trials investigating TKIs in the adjuvant RCC setting have reported to date.

CONTEXT

Key Objective

We designed SORCE to investigate the role of sorafenib in prolonging disease-free survival (DFS) and overall survival (OS) in patients with resected renal cell cancer (RCC) found to be at immediate or high-risk of recurrence.

Knowledge Generated

We observed no benefit for DFS or OS after up to 3 years of sorafenib treatment. Moreover, grade ≥ 3 toxicities were experienced by six in 10 patients who received treatment. A reduction in the initial starting dose improved compliance, but despite offering treatment adaptations, over half of participants stopped treatment by 12 months.

Relevance

SORCE results are definitive; sorafenib should not be used as adjuvant therapy for patients with resected RCC. SORCE is the fifth and final trial to report on the role of tyrosine kinase inhibitor therapy as an adjuvant treatment of RCC. SORCE results confirm that active surveillance remains the global standard of care for patients at intermediate or high risk of recurrence after nephrectomy.

S-TRAC (ClinicalTrials.gov identifier: NCT00375674), ASSURE (ClinicalTrials.gov identifier: NCT00326898), and PROTECT (ClinicalTrials.gov identifier: NCT01235962) explored 1 year of adjuvant TKI therapy, whereas ATLAS (ClinicalTrials.gov identifier: NCT01599754) explored up to 3 years of TKI therapy.[7-10] In S-TRAC, a modest disease-free survival (DFS) benefit with 1 year of sunitinib was observed based on blinded independent central review (hazard ratio [HR], 0.76; 95% CI, 0.59 to 0.98; $P = .03$).[10,11] On the basis of these results, the US Food and Drug Administration approved sunitinib for the adjuvant treatment of patients with RCC at high risk of recurrence. The European Medicines Agency did not approve sunitinib use in this setting. Therefore, these results have not been universally practice changing, and the international standard of care for resected RCC remains nephrectomy followed by active surveillance.[12,13]

The particular value of SORCE is to settle the question of adjuvant TKI therapy. Here, we report findings from the primary analysis of SORCE, comparing participants who were randomly assigned to receive 3 years of sorafenib with those who were randomly assigned to receive placebo. We also report the findings of our analyses of participants randomly assigned to 1 year of sorafenib versus those assigned to placebo.

PATIENTS AND METHODS

Study Design

SORCE (ClinicalTrials.gov identifier: NCT00492258) is an international, double-blind, three-arm, randomized, phase III trial evaluating different durations of adjuvant sorafenib compared with placebo.

Participants

Eligible participants had histologically proven, completely resected, clear cell or non–clear cell RCC at intermediate (score, 3-5) or high risk (score, 6-11) of relapse as per the Leibovich risk model.[14] The Leibovich score is a validated scoring model incorporating TNM stage, tumor size, nuclear grade, and presence of tumor necrosis. Details on the features and calculation of the Leibovich score can be found in Appendix Table A1 (online only). Patients with resected metastatic (M1) disease were not eligible.

Participants were enrolled within 13 weeks of nephrectomy, were ≥ 18 years old, had WHO performance status of 0 or 1, and demonstrated adequate bone marrow, renal, hepatic, and pancreatic function. All participants provided written informed consent.

Randomization and Masking

Participants were randomly assigned (2:3:3) using stratified blocks to receive 3 years of placebo (arm A), 1 year of sorafenib followed by 2 years of placebo (arm B), or 3 years of sorafenib (arm C). SORCE was a double-blind trial. Participants were stratified by country and Leibovich risk group.

Treatment and Follow-Up

The initial starting dose of sorafenib was 400 mg twice daily, with permitted dose reductions in the event of toxicity, first to 400 mg once daily and then to 400 mg on alternate days. In January 2009, we amended the starting dose to 400 mg once daily to address a higher than expected discontinuation rate (protocol version 1.4, November 2008). After 3 weeks of treatment, the dose could be maintained or escalated to the full dose of 400 mg twice daily at clinician discretion. Pill counts were performed at assessment visits to allow assessment of dosing compliance.

Patients were assessed at weeks 3 and 6 after the start of their treatment to identify and treat any early toxicities and every 3 months for adverse events (AEs). Imaging alternated between chest x-ray and contrast computed tomography (CT) of the chest and abdomen every 3 months

during treatment. After completion of treatment, participants had chest x-rays only every 6 months until year 5 and then annually until year 10. Recurrence was assessed by local investigators.

Outcome Measures

The primary outcome measure is DFS, defined as the interval from random assignment to first evidence of local recurrence, distant metastases, or death from RCC. Secondary outcomes included overall survival (OS), defined as the time from randomization to death from any cause; metastasis-free survival (MFS), defined as the time from randomization to first evidence of metastases or death from RCC; RCC-specific survival time; and safety (using CTCAE v3.0). Participants alive and without an event at the time of each time-to-event analysis were censored on the date they were last seen on the trial.

Changing the Primary Research Question

The original primary objective in SORCE was to determine whether at least 1 year of treatment with sorafenib increases DFS compared with placebo (a comparison of arms B and C combined *v* arm A). Primary results from the ASSURE and S-TRAC trials were reported after SORCE closed to recruitment. Considering these results and without knowledge of the developing outcome data, the SORCE Trial Management Group (TMG) and the independent members of the executive oversight Trial Steering Committee approved a change to the primary analysis of SORCE. These changes are documented in our protocol and statistical analysis plan and were all agreed on before database lock.[15]

The revised primary analysis objectives were as follows: Does up to 3 years of treatment with sorafenib increase DFS compared with placebo (a comparison of arm C *v* arm A), and if so, does up to 1 year of sorafenib (arm B) increase DFS compared with placebo (arm A)? A closed testing procedure was used for the second question, which naturally preserves the type I error. If the analysis of the first objective did not show statistical significance, results for the second objective would still be presented for completeness, although no statistical inferences can be drawn.

Study Oversight

The trial was approved by national regulatory and ethical committees in each participating country and was conducted in accordance to the principles of Good Clinical Practice, the Declaration of Helsinki, and all applicable regulatory requirements and laws. An Independent Data Monitoring Committee (IDMC) reviewed participant safety on a regular basis and efficacy data at prespecified time points. An executive Trial Steering Committee received trial reports on at least an annual basis.

Sample Size

The sample size for SORCE was based on the original primary research question. It was calculated using the ART software assuming an HR of 0.75 between arm A and arms B and C combined.[16] We assumed conservatively that the 2 additional years of sorafenib in arm C would not increase DFS compared with arm B. DFS at 3 years for participants in arm A, obtained from Leibovich et al[14] and restricted to the intermediate and poor prognostic groups, was estimated to be 63.5%. To demonstrate a clinically important improvement in 3-year DFS from 63.5% to 71% (HR, 0.75) with sorafenib, using a log-rank test with 90% power and 5% two-sided significance level, required 608 DFS events, 179 of which would be in arm A. The total sample size target was 1,656 participants (414 participants in arm A and 621 in each of arms B and C).

Because recruitment was complete at the time of changing the primary research questions, the sample size was not recalculated. The target number of control arm events remained unchanged at 179 DFS events. With this number of events in the control arm and with all other assumptions unchanged, the study had 86% power to detect an HR of 0.75 at the 5% two-sided significance level. Two subgroup analyses were prepowered before analysis (Appendix, online only)—DFS in participants with a high-risk Leibovich score (score, 6-11) and in participants with clear cell histology.

Interim Assessment by the IDMC

Two planned interim efficacy analyses were performed after approximately 200 and 400 of the planned events had occurred using a stringent two-sided significance level of $P = .001$ at each interim analysis (Peto boundary). The IDMC requested one additional efficacy analysis, which was carried out after approximately 500 events. On each occasion, the IDMC recommended that the trial continue as planned. The final analysis was performed with no adjustment for multiple testing.

Statistical Analysis Plan

A final statistical analysis plan was approved before any analyses were performed. All efficacy analyses were performed on the intent-to-treat (ITT) population. Survival curves were estimated based on the Kaplan-Meier method. Cox proportional hazards models, adjusted for the stratification factors used at randomization, were fitted to the data to obtain the HR and associated CIs. The proportional hazards assumption was tested using the Grambsch-Therneau test based on the ranks of the failure times, using a significance level of $P = .1$ as a guide. Restricted mean survival time (RMST) was emphasized in the presence of nonproportionality, using a time horizon (t^*) of 10 years.[17] The RMST is the area under the survival distribution from 0 to t^* and is interpreted as the life expectancy between randomization ($t = 0$) and a particular time horizon ($t = t*$).[18] To estimate the survival distribution, we fitted flexible parametric models with (3, 1) df and adjusted for the stratification factors and time to event. All tests are presented as two sided, with 95% CIs and relevant

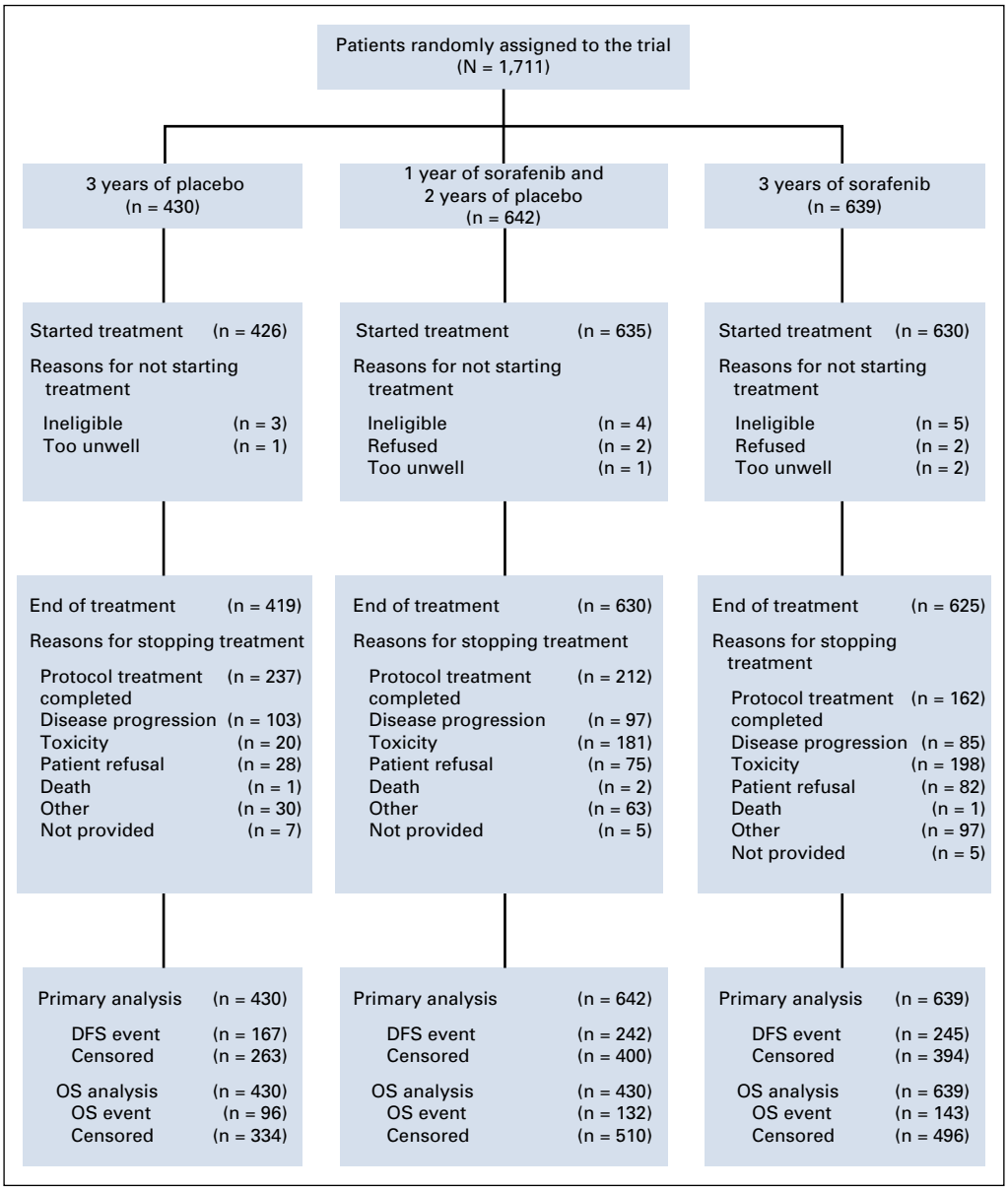

FIG 1. CONSORT diagram. DFS, disease-free survival; OS, overall survival.

P values. AE data are summarized for the safety population, defined as participants who received at least one dose of their allocated trial treatment.

RESULTS

Participants

We randomly assigned 1,711 participants from 147 sites in seven countries between July 24, 2007, and April 12, 2013; 430 participants were assigned to placebo for 3 years (arm A), 642 to sorafenib for 1 year followed by placebo for 2 years (arm B), and 639 to sorafenib for 3 years (arm C). The number of participants who did not receive any drug or placebo were five, 17, and 26 patients in arms A, B, and C, respectively; these participants are included in the ITT analysis for primary efficacy but excluded from the safety analysis (Fig 1). Median follow-up at the time of analysis was 6.5 years (interquartile range [IQR], 4.9-8.0 years). The baseline characteristics of participants are listed in Table 1 and were well balanced across the treatment arms.

DFS

We observed no difference in DFS between patients randomly assigned to 3 years of sorafenib and those assigned to placebo (HR, 1.01; 95% CI, 0.82 to 1.23; $P = .946$; 245 events for 3 years of sorafenib and 167 events for placebo). We observed nonproportional hazards ($P = .042$); the RMST estimate over 10 years was 6.81 years (95% CI, 6.52 to 7.11 years) for 3 years of sorafenib and 6.82 years (95% CI, 6.45 to 7.18 years) for placebo (difference, 0.01 year; $P = .988$).

TABLE 1. Baseline Characteristics

Characteristic	3 Years of Placebo (n = 430)	1 Year of Sorafenib Plus 2 Years of Placebo (n = 642)	3 Years of Sorafenib (n = 639)	All Patients (N = 1,711)
Mean age at random assignment, years (SD)	58.43 (10.35)	58.34 (10.60)	57. 97 (10.86)	58.22 (10.63)
Time from RCC diagnosis to random assignment, days (SD)	84.03 (26.33)	82.24 (31.86)	83.23 (30.65)	83.06 (30.09)
Country				
Australia	42 (10)	62 (10)	64 (10)	168 (10)
Belgium	11 (3)	12 (2)	13 (2)	36 (2)
Denmark	5 (1)	8 (1)	7 (1)	20 (1)
France	32 (7)	45 (7)	45 (7)	122 (7)
The Netherlands	5 (1)	8 (1)	6 (1)	19 (1)
Spain	4 (1)	6 (1)	5 (1)	15 (1)
United Kingdom	331 (77)	501 (78)	499 (78)	1,331 (78)
Sex				
Female	124 (29)	190 (30)	181 (28)	495 (29)
Male	306 (71)	452 (70)	458 (72)	1,216 (71)
WHO status				
0	345 (80)	517 (81)	501 (78)	1,363 (80)
1	83 (19)	121 (19)	131 (21)	335 (20)
2	—	—	1 (0)	1 (0)
Missing	2 (0)	4 (1)	6 (1)	12 (1)
Histology				
Clear cell	361 (84)	534 (83)	550 (86)	1,445 (84)
Papillary	33 (8)	58 (9)	37 (6)	128 (7)
Chromophobe	29 (7)	31 (5)	36 (6)	96 (6)
Collecting duct	1 (0)	2 (0)	1 (0)	4 (0)
Other	6 (1)	17 (3)	15 (2)	38 (2)
Pathologic T stage of primary tumor				
pT1a	3 (1)	2 (0)	2 (0)	7 (0)
pT1b	44 (10)	82 (13)	71 (11)	197 (12)
pT2	103 (24)	154 (24)	143 (22)	400 (23)
pT3a-4	280 (65)	404 (63)	423 (66)	1,107 (65)
Regional lymph node status				
pNx/pN0	412 (96)	619 (96)	606 (95)	1,637 (96)
pN1/pN2	18 (4)	23 (4)	33 (5)	74 (4)
Tumor size, cm				
< 10	286 (67)	436 (68)	430 (67)	1,152 (67)
> 10	144 (33)	206 (32)	209 (33)	559 (33)
Nuclear grade				
1	19 (4)	38 (6)	32 (5)	89 (5)
2	105 (24)	159 (25)	176 (28)	440 (26)
3	222 (52)	323 (50)	314 (49)	859 (50)
4	84 (20)	122 (19)	116 (18)	322 (19)
Missing	—	—	1 (0)	1 (0)

(continued on following page)

TABLE 1. Baseline Characteristics (continued)

Characteristic	3 Years of Placebo (n = 430)	1 Year of Sorafenib Plus 2 Years of Placebo (n = 642)	3 Years of Sorafenib (n = 639)	All Patients (N = 1,711)
Histologic tumor necrosis				
No	192 (45)	284 (44)	298 (47)	774 (45)
Yes	238 (55)	358 (56)	341 (53)	937 (55)
Leibovich score				
3	30 (7)	65 (10)	56 (9)	151 (9)
4	83 (19)	129 (20)	135 (21)	347 (20)
5	111 (26)	148 (23)	153 (24)	412 (24)
6	99 (23)	139 (22)	131 (21)	369 (22)
7	48 (11)	73 (11)	80 (13)	201 (12)
8	30 (7)	53 (8)	48 (8)	131 (8)
9	24 (6)	32 (5)	26 (4)	82 (5)
10	3 (1)	1 (0)	4 (1)	8 (0)
11	2 (0)	2 (0)	6 (1)	10 (1)
Leibovich score group				
Intermediate	224 (52)	342 (53)	344 (54)	910 (53)
High	206 (48)	300 (47)	295 (46)	801 (47)

NOTE. Data presented as No. (%), unless otherwise indicated.
Abbreviations: RCC, renal cell carcinoma; SD, standard deviation.

Comparing 1 year of sorafenib versus placebo, we also observed no difference in DFS (HR, 0.94; 95% CI, 0.77 to 1.14; $P = .509$; 245 events for 1 year of sorafenib and 167 events for placebo). Again, nonproportional hazards were evident ($P = .001$). The RMST estimate over 10 years was 6.98 years (95% CI, 6.70 to 7.27 years) for 1 year of sorafenib and 6.79 years (95% CI, 6.43 to 7.16 years) for placebo (difference, 0.19 year; $P = .422$).

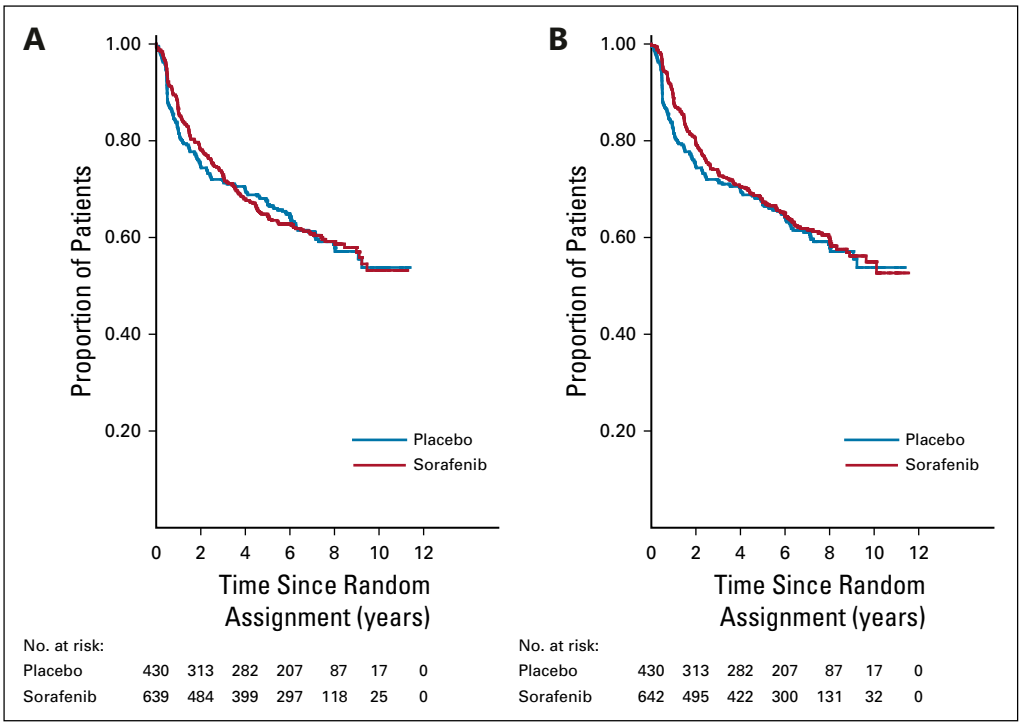

FIG 2. Disease-free survival in patients randomly assigned to (A) 3 years of sorafenib versus placebo and (B) 1 year of sorafenib versus placebo.

TABLE 2. Cause of Death by Treatment Arm

Cause of Death	No. of Patients		
	Placebo	1 Year of Sorafenib	3 Years of Sorafenib
Disease related	77	105	122
Protocol treatment related	0	1[a]	0
Other cause	17	25	20
Missing	2	1	1
Total	96	132	143

[a]For more information, see Fairfax et al.[22]

Median DFS was not reached in any of the arms in SORCE. Ten-year DFS rate was 54% for placebo, 53% for 3 years of sorafenib and 55% for 1 year of sorafenib (Fig 2).

OS

At the time of analysis, 371 patients had died; the causes of death are listed in Table 2 and Appendix Table A2 (online only). No difference in duration of OS was observed (3 years of sorafenib *v* placebo: HR, 1.06; 95% CI, 0.82 to 1.38; $P = .638$; 1 year of sorafenib *v* placebo: HR, 0.92; 95% CI, 0.71 to 1.20; $P = .541$). Proportional hazards were observed, so as per our statistical analysis plan, we have not reported RMST. Ten-year OS rate was 69% for placebo, 70% for 3 years of sorafenib, and 69% for 1 year of sorafenib (Fig 3).

Preplanned DFS Subgroup Analyses

We observed no difference in DFS for either 3 years or 1 year of sorafenib compared with placebo in our two preplanned and prepowered analyses in participants with Leibovich high-risk disease and in those with clear cell RCC or in our modified DFS population (Appendix Tables A3 and A4 and Figs A1 and A2, online only).

AEs and Safety

In total, 1,663 (97%) of 1,711 patients started treatment and are included in the safety analysis (placebo, n = 425; 1 year of sorafenib, n = 625; and 3 years of sorafenib, n = 613). Almost all patients in the safety population had at least one AE of any grade (99%). At least one grade ≥ 3 AE was reported by 366 patients (58.6%) receiving 1 year of sorafenib, 392 patients (63.9%) receiving 3 years of sorafenib, and 124 patients (29.2%) receiving placebo. The proportion of patients who experienced at least one serious AE (SAE) was 19.1% for placebo, 21.6% for 1 year of sorafenib, and 24% for 3 years of sorafenib. Table 3

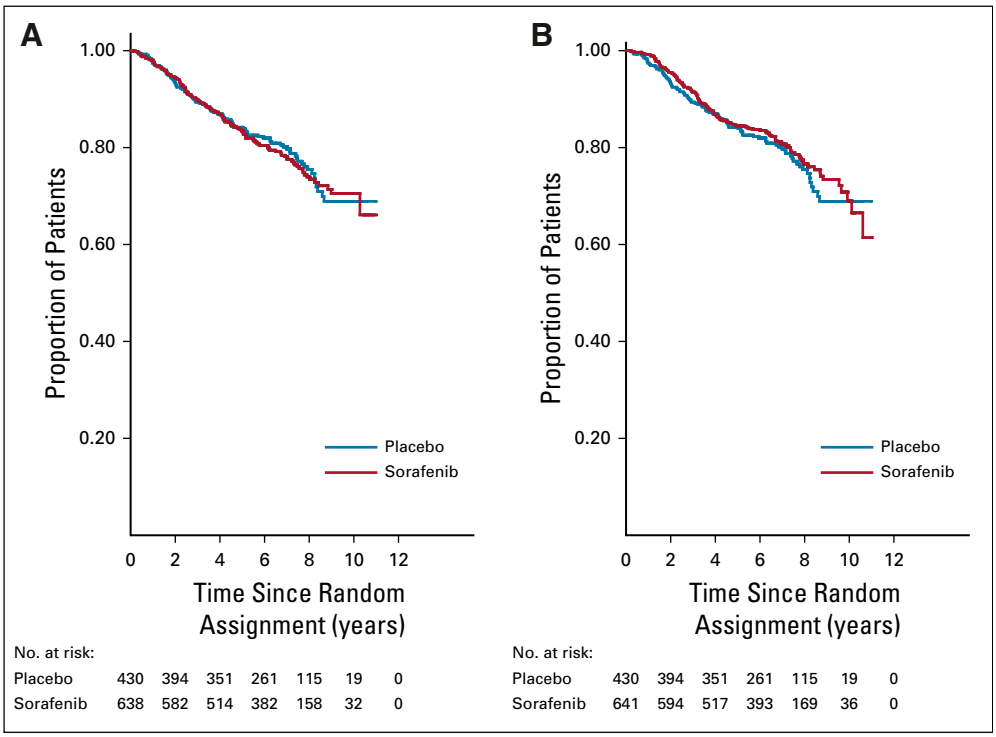

FIG 3. Overall survival in patients randomly assigned to (A) 3 years of sorafenib versus placebo and (B) 1 year of sorafenib versus placebo. The figures have been truncated at 11 years.

TABLE 3. Patients in the Safety Population Who Experienced AEs and Serious AEs and the Worst Grade AE Reported

AE	Placebo	1 Year of Sorafenib	3 Years of Sorafenib
Any grade AE (at least one), No. (%)	414 (97.4)	625 (100)	608 (99.2)
Grade ≥ 3 AE (at least one), No. (%)	124 (29.2)	366 (58.6)	392 (63.9)
At least one serious AE	81 (19.1)	135 (21.6)	147 (24)
Adverse event, %[a]			
Rash			
Any grade	30	70	71
Grade 3	0	7	10
Grade 4	0	0	0
Diarrhea			
Any grade	32	61	64
Grade 3	1	6	6
Grade 4	0	0	0
Hand-foot syndrome			
Any grade	32	79	77
Grade 3	0	24	24
Grade 4	0	0	0
Fatigue			
Any grade	60	74	74
Grade 3	2	4	4
Grade 4	0	0	0
Nausea			
Any grade	26	34	30
Grade 3	1	1	0
Grade 4	0	0	0
Hypertension			
Any grade	48	60	64
Grade 3	20	26	24
Grade 4	0	0	0
Alopecia			
Any grade	12	54	49
Grade 3	0	0	0
Grade 4	0	0	0
Other			
Any grade	87	88	89
Grade 3	9	12	17
Grade 4	1	1	2

Abbreviation: AE, adverse event.

[a]Percentages are based on the number of patients in the safety population in each arm.

provides a breakdown of AEs and SAEs by arm. Worst grade of AEs reported in each of the three arms is also listed in Table 3. Notable toxicities were hand-foot skin reactions and hypertension.

Other Secondary Outcome Measures

Results from the analyses of both MFS and RCC-specific survival time are provided in the Appendix (Appendix Tables A5 and A6 and Figs A3 and A4, online only). Results from the TRANSORCE studies completed to date and our patient and clinician preferences for adjuvant sorafenib substudies are reported separately.[19,20]

Dose Delivered and Duration of Therapy

Two hundred twenty-six participants (13%) started treatment on the full dose of 400 mg twice daily; the remaining

TABLE 4. Reasons Patients Stopped Treatment in the SORCE Trial

Reason for Stopping Treatment	% of Patients		
	Placebo	1 Year of Sorafenib	3 Years of Sorafenib
Protocol treatment completed	55	33	25
Disease progression	24	15	13
Excessive toxicity	4	30	34
Patient refusal	8	14	15
Clinical decision/other medical condition	3	6	9
New primary cancer	1	1	1
Death	0.2	0.3	0.2
Other (error/administrative reasons)	1	1	2
Missing	2	1	1

participants (n = 1,485, 87%) started treatment on an initial dose of 400 mg once daily for the first 3 weeks, which could be extended for longer if required. Dose reductions in the event of significant toxicity and subsequent re-escalation on resolution were permitted. As in the other adjuvant TKI trials in patients with RCC and despite the permitted dose modifications, many participants did not complete their assigned protocol treatment, even in the placebo arm. Approximately half of participants had withdrawn from treatment by the end of the first year in both treatment arms (Appendix Table A7, online only). We present time to discontinuation or termination of treatment in Appendix Figure A5 (online only). Appendix Figure A6 (online only) presents months on treatment against total pill count for each treatment arm, graphically illustrating that patients found it difficult to comply with protocol treatment and many patients ended treatment prematurely.

Median number of months on treatment was 35.4 months (IQR, 11.4-35.9 months) for placebo, 11.7 months (IQR, 1.9-35.6 months) for 1 year of sorafenib, and 10.6 months (IQR, 2.3-35.2 months) for 3 years of sorafenib. The reduced starting dose, although introduced quite early on in the trial, had little overall effect on the median (or mean) number of months on treatment (Appendix Table A8, online only). Reasons for stopping treatment are listed in Table 4.

Treatment on Recurrence

The number of participants in each arm who received additional systemic treatment after progression was similar in each of the arms (Appendix Table A9, online only).

DISCUSSION

SORCE was an international, phase III trial investigating sorafenib, an oral multikinase inhibitor, in patients with resected RCC at intermediate or high risk of recurrence and including all histologic subtypes. We observed no difference in DFS for either 3 years or 1 year of sorafenib compared with placebo in the overall trial population, the Leibovich high-risk participants, or participants with clear cell RCC. Similarly, we showed no difference in duration of OS between participants who received 3 years or 1 year of sorafenib versus placebo. We did not observe proportional hazards; we found an apparent separation between the curves, but it does not support further investigation when the overall results are so definitive.

Our results are in line with those from the ASSURE trial, which showed no benefit of 1 year of sunitinib or sorafenib compared with placebo (DFS: HR, 1.02 [97.5% CI, 0.85 to 1.23] and 0.97 [97.5% CI, 0.80 to 1.17] for sunitinib and sorafenib, respectively).[8] They are also in line with the PROTECT and ATLAS trial results.[7,9] S-TRAC was the only study to show a modest DFS benefit with 1 year of sunitinib (HR, 0.76; 95% CI, 0.59 to 0.98; $P = .03$) but only when DFS events were subject to blinded independent central review; no improvement in OS was observed.[10,11] Appendix Table A10 (online only) summarizes the inclusion criteria and risk scores used in these trials.

Drug toxicity and the resultant reticence of participants to stay on treatment were observed in all of the adjuvant TKI trials; SORCE was no different. We amended the SORCE protocol after < 18 months of accrual. The TMG had noticed that many patients were stopping treatment as a result of toxicity (particularly skin rash). Our IDMC encouraged an amendment when they reviewed the unblinded data in October 2008. We submitted an amended protocol for ethics and regulatory approval in November 2008, and the change was implemented at sites in January 2009.

Despite reducing the initial dose for the first 3 weeks, allowing flexibility in the requirement for escalation to full standard dose, and encouraging dose reductions to mitigate toxicity, only 33% and 25% of SORCE participants completed 1 and 3 years of protocol treatment, respectively. Approximately half of participants had withdrawn from treatment by the end of the first year in both treatment arms, with excessive toxicity and patient refusal cited as the dominant reasons for stopping. In SORCE,

grade ≥ 3 AEs were reported in 59%-64% of participants on treatment, which is comparable to findings in other TKI trials. Hand-foot skin reaction and hypertension caused the most grade 3 events in the 1- and 3-year cohorts, which we were unable to mitigate with our dosing strategy. Ultimately, the high AE rates leading to dose reductions and early stoppages, seen across all adjuvant TKI trials, are likely to have affected the efficacy of TKIs in this setting. An exploratory analysis conducted as part of a systematic review and pooled analysis of trial data from SORCE, ASSURE, and PROTECT suggests that participants who started on full dose may have an improved DFS (HR_{random}, 0.83; 95% CI, 0.73 to 0.95; $P = .005$).[13] However, this is exactly the limiting factor because full-dose treatment was only achieved in a minority of participants who took part in any of the VEGF-targeted adjuvant trials.

The risk-benefit profile of additional treatment is an essential consideration in patients receiving treatment and experiencing toxicity in the adjuvant setting without overt metastatic disease. The significant toxicity observed with TKI monotherapy, despite pragmatic dose reductions, together with lack of evidence of a survival benefit, fundamentally undermines the use of TKIs in the adjuvant treatment of RCC. The results from our patient preferences for an adjuvant sorafenib substudy support this observation. Treatment duration and the toxicity patients experienced were both important determinants of patients' preferences for adjuvant sorafenib. A typical participant who had been treated with adjuvant sorafenib judged that to warrant continuing it for 3 years, a median survival gain of an additional 9-12 months would be required, above and beyond the 9-12 months required to make the initial 1 year of adjuvant therapy worthwhile.[21]

In SORCE, imaging alternated between chest x-ray and contrast CT of the chest and abdomen every 3 months during treatment. After completion of treatment, participants had chest x-rays only every 6 months until year 5 and then annually until year 10, but with advice to confirm clinical signs of recurrence via CT or x-ray or a positive biopsy. This was different from the other TKI trials, which used CT scans or magnetic resonance imaging throughout. Of our 654 disease recurrence events, 547 were reported on CT scan, only nine were reported on chest x-ray, and 77 were reported using mixed modalities or biopsies (information is missing for 21 participants). Method of assessment was similar across arms.

Effective adjuvant therapy for patients who have had their primary renal cancer removed by surgery remains an unmet clinical need. The international infrastructure developed to conduct SORCE over the years has paved the way for our current adjuvant trial RAMPART (ClinicalTrials.gov identifier: NCT03288532), a University College London–sponsored multiarm, multistage platform trial investigating single-agent durvalumab (anti–programmed death ligand-1) and durvalumab in combination with tremelimumab (anti–cytotoxic T-lymphocyte–associated protein 4). Numerous other adjuvant trials investigating immune checkpoint inhibitors either as monotherapies or in combination are ongoing and will report over the coming years.

The results from SORCE unequivocally confirm that sorafenib should not be used as adjuvant therapy for patients with resected RCC at intermediate or high risk of relapse. We observed no DFS or OS benefit for up to 3 years of sorafenib treatment in this patient group, yet participants experienced a range of treatment-associated toxicities. Active surveillance remains the global standard of care for patients at intermediate or high risk of recurrence after nephrectomy and is the appropriate control arm of our current international adjuvant RCC trial, RAMPART.

AFFILIATIONS

[1]Department of Oncology, Cambridge University Hospitals National Health Service (NHS) Foundation Trust, Cambridge, United Kingdom
[2]Medical Research Council Clinical Trials Unit at University College London (UCL), Institute of Clinical Trials and Methodology, London, United Kingdom
[3]Monash University and Eastern Health, Box Hill, Victoria, Australia
[4]National Health and Medical Research Council Clinical Trials Centre, Central Clinical School, Department of Medicine, University of Sydney, Sydney, New South Wales, Australia
[5]Institut Gustave Roussy, Villejuif, France
[6]The Royal Marsden Hospital, London, United Kingdom
[7]Royal Free London NHS Foundation Trust UCL, Division of Surgery and Interventional Science, London, United Kingdom
[8]Netherlands Cancer Institute, Amsterdam, the Netherlands
[9]Department of Development and Regeneration, Urogenital, Abdominal, and Plastic Surgery, University Hospitals Leuven, Leuven, Belgium
[10]University of Sheffield, Academic Unit of Clinical Oncology, Weston Park Cancer Centre, Sheffield, United Kingdom
[11]Urology Research Unit, Department of Urology, Herlev/Gentofte Hospital, Herlev, Denmark
[12]Beth Israel Deaconess Medical Center-IMIM Research Lab, Boston, MA
[13]Pharmacy Department, Weston Park Hospital, Sheffield, United Kingdom
[14]Department of Surgery, University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom
[15]Velindre Cancer Centre, Cardiff, United Kingdom
[16]Academic Unit of Clinical Oncology, Weston Park Hospital, University of Sheffield, Sheffield, United Kingdom
[17]Institute of Cancer and Pathology, St James's University Hospital, University of Leeds, Leeds, United Kingdom
[18]Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, United Kingdom
[19]Mount Vernon Cancer Centre, Northwood, United Kingdom

DISCLAIMER

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CORRESPONDING AUTHOR

Tim Eisen, MB BChir, PhD, Department of Oncology, Cambridge University Hospitals NHS Foundation Trust, Box 193 (R4), Addenbrooke's Hospital, Cambridge Biomedical Campus, Hill's Road, Cambridge CB2 0QQ, United Kingdom; e-mail: tgqe2@medschl.cam.ac.uk.

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AUTHOR CONTRIBUTIONS

Conception and design: Tim Eisen, Alastair W.S. Ritchie, Ian D. Davis, Martin R. Stockler, Bernard Escudier, Barry Hancock, Joaquim Bellmunt, Elizabeth Hodgkinson, Janet Brown, Angela Meade
Administrative support: Benjamin Smith, Martin R. Stockler, Gregers G. Hermann, Angela Meade
Provision of study materials or patients: Tim Eisen, Ian D. Davis, Laurence Albiges, Martin R. Stockler, Bernard Escudier, James Larkin, Axel Bex, Gregers G. Hermann, Joaquim Bellmunt, Jim Barber, Janet Brown, Rhona McMenemin, Paul Nathan, Lisa M. Pickering
Collection and assembly of data: Alastair W.S. Ritchie, Benjamin Smith, Rick Kaplan, Ian D. Davis, Martin R. Stockler, Laurence Albiges, Steven Joniau, Gregers G. Hermann, Joaquim Bellmunt, Jim Barber, Janet Brown, Rhona McMenemin, Angela Meade
Data analysis and interpretation: Tim Eisen, Eleni Frangou, Bhavna Oza, Alastair W.S. Ritchie, Rick Kaplan, Ian D. Davis, Martin R. Stockler, Laurence Albiges, Bernard Escudier, James Larkin, Axel Bex, Steven Joniau, Joaquim Bellmunt, Grant D. Stewart, Janet Brown, Paul Nathan, Lisa M. Pickering, Mahesh K.B. Parmar, Angela Meade
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

DEDICATION

We dedicate this article to Pat Hanlon and Martin Gore. Pat was our patient and public involvement representative on the trial management group, who sadly died in January 2020. Martin was a friend and mentor to many of us as well as being an excellent medical oncologist who constantly shouted encouragement from the sidelines. Both Martin and Pat had a huge commitment to kidney cancer research, and we miss them very much.

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Tim Eisen
Employment: AstraZeneca, Roche
Leadership: AstraZeneca, Roche
Stock and Other Ownership Interests: AstraZeneca, AstraZeneca (I)
Honoraria: EUSA
Consulting or Advisory Role: EUSA
Research Funding: Bayer (Inst), Pfizer (Inst), AstraZeneca (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Roche
Other Relationship: Macmillan Cancer Support, Kidney Cancer UK

Richard Kaplan
Research Funding: AstraZeneca (Inst)

Ian D. Davis
Research Funding: Astellas Pharma (Inst), Pfizer (Inst), Genentech (Inst), MSD Oncology (Inst), AstraZeneca (Inst), Janssen Oncology (Inst), Eisai (Inst), Bayer (Inst), Amgen (Inst), Bristol Myers Squibb (Inst), Movember Foundation (Inst), Exelixis (Inst), Ipsen (Inst), Medivation (Inst)
Patents, Royalties, Other Intellectual Property: International Patent Application No: PCT/US2004/032147 (NY-ESO-1) through Ludwig Institute for Cancer Research

Martin R. Stockler
Research Funding: Astellas Pharma (Inst), Celgene (Inst), Bayer (Inst), Bionomics (Inst), Medivation (Inst), Sanofi (Inst), Pfizer (Inst), AstraZeneca (Inst), Bristol Myers Squibb (Inst), Roche (Inst), Amgen (Inst), Merck Sharp & Dohme (Inst), Tilray (Inst)
Travel, Accommodations, Expenses: Medivation/Pfizer

Laurence Albiges
Consulting or Advisory Role: Novartis (Inst), Amgen (Inst), Bristol Myers Squibb (Inst), Ipsen (Inst), Roche (Inst), Novartis (Inst), Pfizer (Inst), Astellas Pharma (Inst), Merck (Inst), MSD (Inst), AstraZeneca (Inst), Exelixis (Inst), Corvus Pharmaceuticals (Inst), Peloton Therapeutics (Inst)
Research Funding: Bristol Myers Squibb (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb, MSD

Bernard Escudier
Honoraria: Pfizer, Novartis, Bristol Myers Squibb, Ipsen, Genentech, EUSA Pharma, Oncorena
Consulting or Advisory Role: Novartis, Pfizer, Bristol Myers Squibb, Ipsen, EUSA Pharma, AVEO Pharmaceuticals, Genentech
Research Funding: Bristol Myers Squibb France (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb, Pfizer, Genentech, Ipsen, MSD

James Larkin
Honoraria: Eisai, Bristol Myers Squibb, MSD, GlaxoSmithKline, Pfizer, Novartis, Genentech, Pierre Fabre, EUSA Pharma, Achilles Therapeutics, AstraZeneca, Boston Biomedical, Ipsen, Imugene, Incyte, iOnctura, Merck Serono, Nektar, Vitaccess, Kymab, Secarna
Consulting or Advisory Role: Eisai, Bristol Myers Squibb, MSD, GlaxoSmithKline, Pfizer, Novartis, Genentech, Pierre Fabre, EUSA Pharma, Achilles Therapeutics, AstraZeneca, Boston Biomedical, Ipsen, Imugene, Incyte, iOnctura, Merck Serono, Nektar, Vitaccess, Secarna, Kymab
Research Funding: Pfizer (Inst), Novartis (Inst), MSD (Inst), Bristol Myers Squibb (Inst), Achilles Therapeutics (Inst), Roche (Inst), Nektar (Inst), Covance (Inst), Immunocore (Inst), AVEO Pharmaceuticals (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb, Pfizer, Novartis, Genentech, AstraZeneca, Boston Biomedical, Incyte, GlaxoSmithKline, Pierre Fabre, Merck Serono

Axel Bex
Consulting or Advisory Role: Pfizer (Inst), Novartis (Inst), Bristol Myers Squibb (Inst), Ipsen (Inst), Eisai (Inst), Genentech (Inst)
Speakers' Bureau: Pfizer, Novartis, Bristol Myers Squibb
Research Funding: Pfizer (Inst)

Steven Joniau
Consulting or Advisory Role: Janssen, AstraZeneca, Bayer, Astellas Pharma
Speakers' Bureau: Astellas Pharma, Janssen, Ipsen
Research Funding: Janssen (Inst), Astellas (Inst), Ipsen (Inst), Bayer (Inst), Ferring (Inst)
Travel, Accommodations, Expenses: Janssen, Ipsen, Astellas Pharma

Joaquim Bellmunt
Stock and Other Ownership Interests: Rainier
Honoraria: UpToDate
Consulting or Advisory Role: Pierre Fabre, Astellas Pharma, Pfizer, Merck, Genentech, Novartis, AstraZeneca/MedImmune, Bristol Myers Squibb
Research Funding: Millennium (Inst), Sanofi (Inst), Pfizer/EMD Serono (Inst)
Travel, Accommodations, Expenses: Pfizer, MSD Oncology, Ipsen

Grant D. Stewart
Honoraria: Pfizer, Merck, EUSA Pharma
Consulting or Advisory Role: CMR Surgical
Research Funding: Pfizer, AstraZeneca

Janet Brown
Consulting or Advisory Role: Novartis, Bayer, Amgen, Ipsen, MSD Oncology
Research Funding: Amgen (Inst), Bayer (Inst)
Travel, Accommodations, Expenses: Ipsen, MSD Oncology, Amgen, Novartis, Bayer

Rhona McMenemin
Honoraria: Janssen Oncology, EUSA Pharma
Consulting or Advisory Role: Ipsen, EUSA Pharma
Speakers' Bureau: EUSA Pharma
Travel, Accommodations, Expenses: EUSA Pharma, Janssen Oncology

Paul Nathan
Consulting or Advisory Role: AstraZeneca, Bristol Myers Squibb, MSD, Immunocore, Pfizer, Pierre Fabre, Novartis, GlaxoSmithKline, Ipsen, 4SC, Merck
Speakers' Bureau: Bristol Myers Squibb, Novartis, MSD, Merck
Travel, Accommodations, Expenses: Bristol Myers Squibb, MSD

Lisa M. Pickering
Consulting or Advisory Role: Pfizer, Ipsen, Bristol Myers Squibb, Eisai, MSD Oncology
Speakers' Bureau: Pfizer, Bristol Myers Squibb
Honoraria: Pfizer, EUSA Pharma, Ipsen, MSD Oncology, Bristol Myers Squibb
Consulting or Advisory Role: Pfizer, Astellas Pharma, EUSA Pharma, MSD Oncology, Bristol Myers Squibb
Research Funding: Pierre Fabre
Travel, Accommodations, Expenses: Bristol Myers Squibb, Ipsen

Angela Meade
Research Funding: AstraZeneca (Inst)

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APPENDIX

Subgroup Analyses

Power to analyze whether up to 3 years of sorafenib increases disease-free survival compared with placebo was calculated based on event rates estimated from published data (STRAC, ASSURE, and ATLAS). With 506 participants with a high-risk Leibovich score in arms A and C and assuming an event rate of 53%, we had 65% power to detect a hazard ratio (HR) of 0.75 at the 5% two-sided significance level. Similarly, with 898 participants with clear cell histology in arms A and C and assuming an event rate of 47%, we had 84% power to detect an HR of 0.75 at the 5% two-sided significance level.

Participating Institutions

The following institutions participated in the study (with lead investigator at each site): Velindre Hospital, Dr Jim Barber; Addenbrooke's Hospital, Prof Tim Eisen; St James University Hospital, Dr Janet Brown; Freeman Hospital, Dr Rhona McMenemin; Mount Vernon Hospital, Dr Paul Nathan; Weston Park Hospital, Dr Omar Din; Cheltenham General Hospital, Dr David Farrugia; Royal Marsden Hospital, Prof Martin Gore; James Cook University Hospital, Dr Alison Humphreys; Leicester General Hospital, Dr Subramanian Vasanthan; Beatson West of Scotland Cancer Centre, Dr Rob Jones; Clatterbridge Centre for Oncology, Dr Richard Griffiths; Queen Alexandra Hospital, Dr Joanna Gale; Royal Derby Hospital, Dr Prabir Chakraborti; Royal Free Hospital, Dr Ekaterini Boleti; Christie Hospital, Dr Tom Waddell; Kent and Canterbury Hospital, Dr Natasha Mithal; Royal Perth Hospital, Dr Simon Troon; Bristol Haematology and Oncology Centre, Dr Amit Bahl; Norfolk and Norwich University Hospital, Dr Rob Wade; Birmingham City Hospital, Dr Daniel Ford; Lincoln County Hospital, Dr Miguel Panades; Castle Hill Hospital, Dr Anthony Maraveyas; St Bartholomews Hospital, Dr Jonathon Shamash; Rigshospitalet University Hospital, Dr Gregers Hermann; University Hospital Coventry and Warwickshire, Dr Jane Worlding; Universitaire Ziekenhuizen Leuven, Prof Hein van Poppel; Derriford Hospital, Dr Martin Highley; Austin Hospital, Prof Ian Davis; Centre Hospitalier Universitaire de Besançon, Dr Antoine Thiery-Vuillemin; Institut Gustave-Roussy, Prof Bernard Escudier; Ipswich Hospital, Dr Christopher Scrase; Royal Stoke University Hospital, Dr Fawzi Adab; Royal Shrewsbury Hospital, Dr Narayanan Srihari; Royal Devon and Exeter Hospital, Dr Rajaguru Srinivasan; Southend University Hospital, Dr Imtiaz Ahmed; Northampton General Hospital, Dr Mario Uccello; Royal Bournemouth Hospital, Dr Tom Geldart; Scunthorpe General Hospital, Dr Sanjay Dixit; Erasmus MC, Dr Willem Harm Jan Kruit; Centre Alexis Vautrin, Dr Lionnel Geoffrois; Institut Paoli Calmettes, Dr Gwenaelle Gravis; Glan Clwyd Hospital, Dr Carey Macdonald-Smith; Prince of Wales Hospital, Dr Elizabeth Hovey; Southampton General Hospital, Dr Matthew Wheater; St George's Hospital, Dr Lisa Pickering; Maidstone Hospital, Dr Sharon Beesley; Wexham Park Hospital, Dr Nicola Dallas; Westmead Hospital, Prof Howard Gurney; Churchill Hospital, Prof Andrew Protheroe; Dorset County Hospital, Stephen Andrews; Nottingham University Hospital, Prof Poulam Patel; Weston General Hospital, Dr Serena Hilman; Royal Brisbane & Women's Hospital, Dr Jeffrey Goh; Darent Valley Hospital, Sanjeev Madaan; Diana Princess of Wales Hospital, Dr Sanjay Dixit; King's Mill Hospital, Dr Santhanam Sundar; Fremantle Hospital, Dr Phillip Claringbold; Canberra Hospital, Dr Desmond Yip; Royal Prince Alfred Hospital, Dr Michelle Harrison; Basildon Hospital, Dr Awais Jalil; Royal Berkshire Hospital, Dr Helen O'Donnell; Torbay District General Hospital, Dr Anna Lydon; Institut de Cancerologie de la Loire, Dr Aline Guillot; Aberdeen Royal Infirmary, Dr Graham MacDonald; Belfast City Hospital, Dr Seamus McAleer; Charing Cross Hospital, Dr Naveed Sarwar; Poole Hospital, Dr Tom Geldart; Queen's Hospital, Dr Mike Smith-Howell; Southmead Hospital, Raj Persad; Worcestershire Royal Hospital, Dr Lisa Capaldi; The Alfred, Dr Sanjeev Gill; Onze Lieve Vrouwziekenhuis, Dr Paul Carpentier; Hôpital Saint-Andre, Dr Alain Ravaud; Centre Hospitalier Universitaire de Rouen, Prof Christian Pfister; Great Western Hospital, Dr Omar Khan; Guy's Hospital, Dr Simon Chowdhury; Pilgrim Hospital, Dr Miguel Panades; Queen Elizabeth Queen Mother Hospital, Dr Natasha Mithal; Salisbury District Hospital, Dr Adityanarayan Bhatnagar; Warwick Hospital, Dr Andrew Chan; Flinders Medical Centre, Dr Ganessan Kichenadasse; Royal Adelaide Hospital, Dr Nimit Singhal; Concord Hospital, Prof Martin Stockler; University Hospital Gent, Prof Sylvie Rottey; Institut Claudius Regaud, Dr Christine Chevreau; Salford Royal Hospital, Prof Noel Clarke; William Harvey Hospital, Dr Natasha Mithal; Box Hill, Dr Joseph McKendrick; Royal North Shore Hospital, Dr Nick Pavlakis; Hôpital Nord, Dr Marjorie Baciuchka; Broomfield Hospital, Dr Gopalakrishnan Srinivasan; South Tyneside District Hospital, Dr Ashraf Azzabi; Western General Hospital, Dr Duncan McLaren; Wycombe Hospital, Dr Prabir Chakraborti; Ysbyty Gwynedd, Dr Anna Mullard; Hospital Ramon y Cajal, Dr Maria Lopez; James Paget Hospital, Dr Rob Wade; Stafford General Hospital, Dr Rajanee Bhana; Sunderland Royal Hospital, Dr Ashraf Azzabi; Sir Charles Gairdner Hospital, Dr Siobhan Ng; Port Macquarie Base Hospital, Dr Stephen Begbie; Radboud University Nijmegen Medical Centre, Prof Peter Mulders; Centre Jean Perrin, Dr Hakim Mahammedi; Centre Hospitalier Universitaire de Limoges, Dr Aurelien Descazeaud; Instituto Valenciano Oncología, Dr Miguel Climent; Alexandra Hospital, Dr Lisa Capaldi; Conquest Hospital, Dr Kathryn Lees; Musgrove Park Hospital, Dr John Graham; Queen Elizabeth Hospital, Dr Anjali Zarkar; Royal United Hospital, Dr Mark Beresford; Border, Dr Craig Underhill; Peninsula Oncology Centre, Dr Vinod Ganju; Centre Léon Bérard, Prof Sylvie Negrier; Centre Paul Papin, Dr Remy Delva; Hospital del Mar, Dr Joaquim Bellmunt; Essex County Hospital, Dr Dakshinamoorthy Muthukumar; Scarborough General Hospital, Simon Hawkyard; St Richard's Hospital, James Hicks; Royal Hobart Hospital, Dr Louise Nott; Jules Bordet Institute, Dr Thierry Gil; Fundació Puigvert, Dr Joan Palou; Whipps Cross University Hospital, Dr Thomas Powles; Yeovil District Hospital, Tim Porter; Centre George-Francois Leclerc, Dr Sylvain Ladoire; Clinique Valdegour, Dr Eric Legouffe; Val d'Aurelle, Dr Diego Tosi; Centre Hospitalier Aix-en-Provence, Dr Sophie Nahon; Clinica Universitaria Navarra, Dr Jose Perez-Gracia.

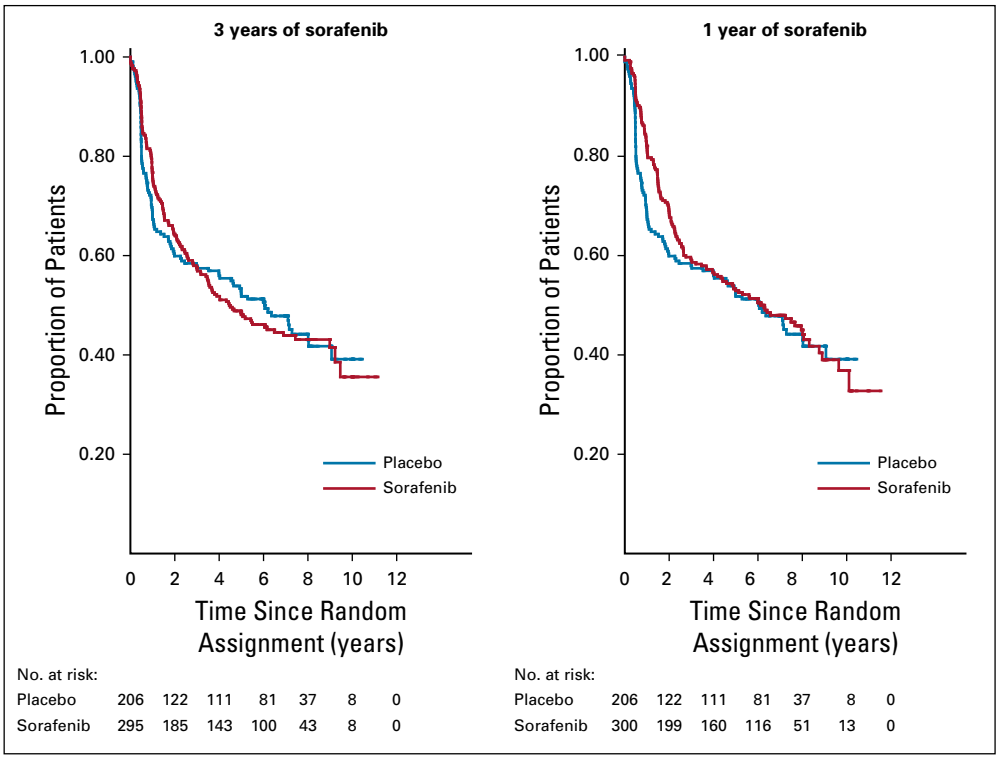

FIG A1. Kaplan-Meier curves of the prespecified and prepowered disease-free survival analyses in Leibovich high-risk patients.

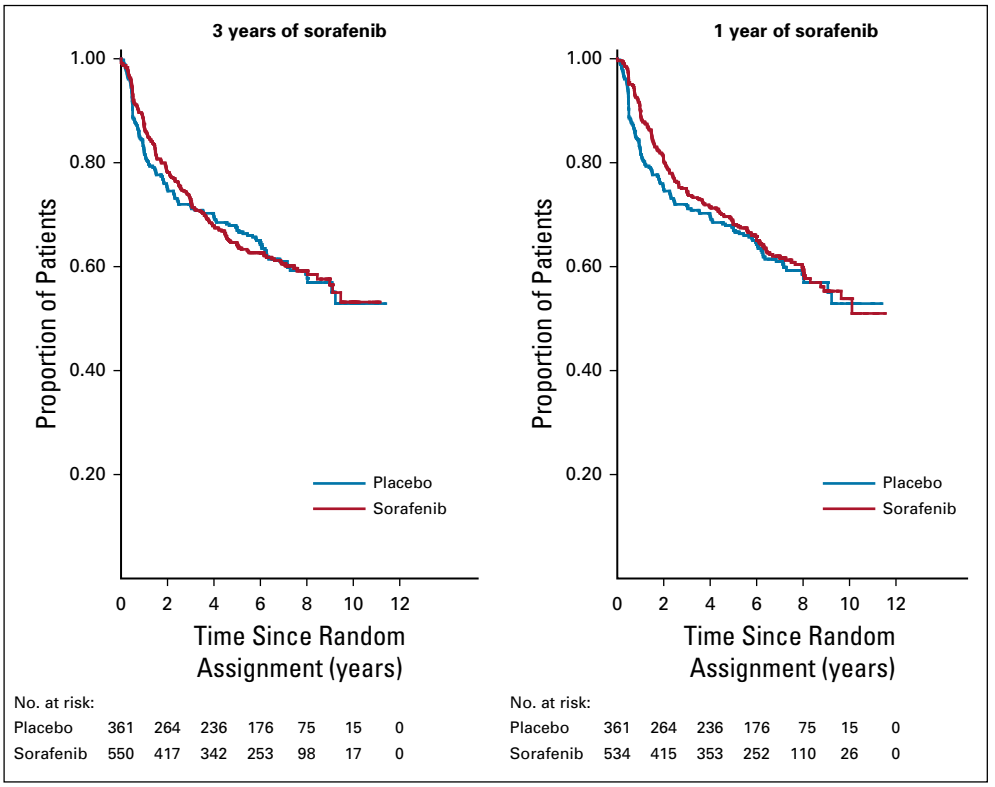

FIG A2. Kaplan-Meier curves of the prespecified and prepowered disease-free survival analyses in patients with clear cell renal cell carcinoma.

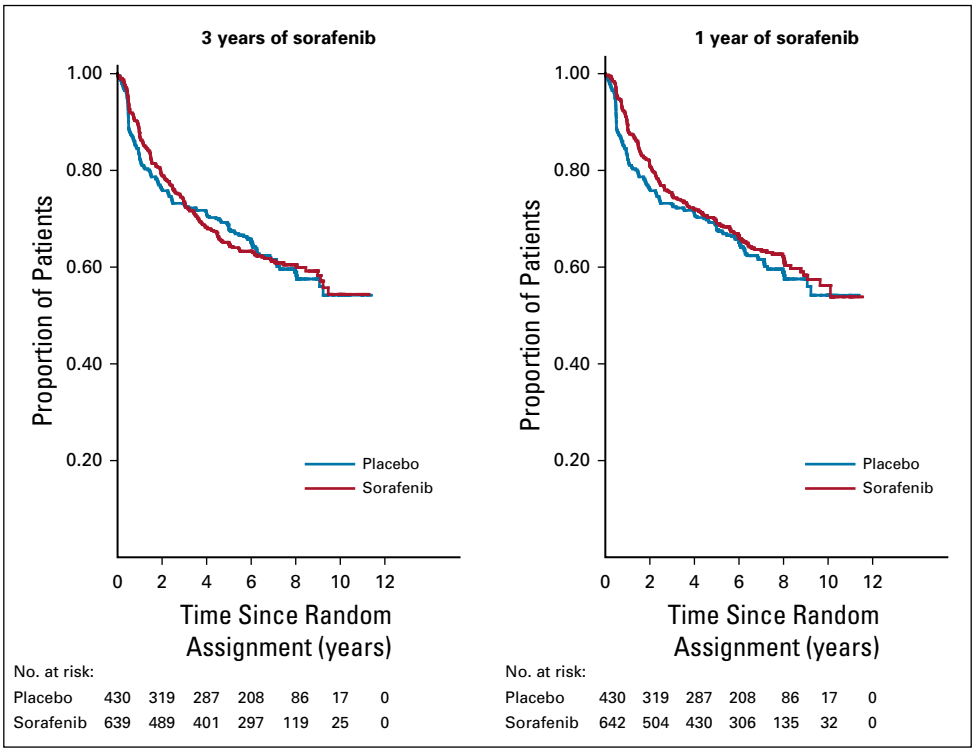

FIG A3. Kaplan-Meier curves for metastasis-free survival.

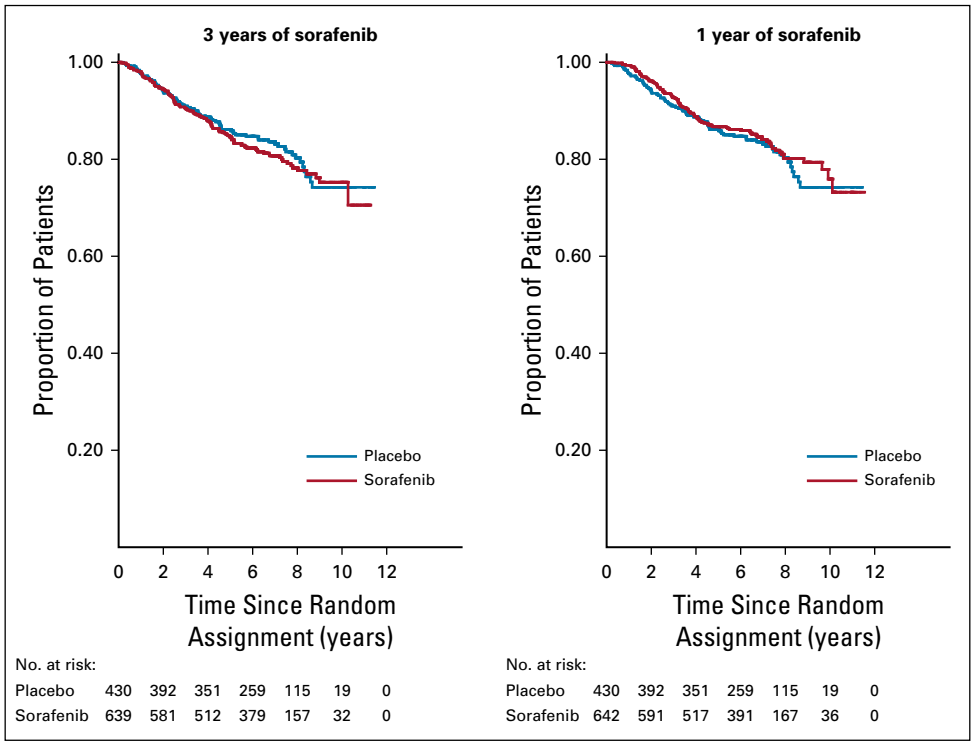

FIG A4. Kaplan-Meier curves for renal cell carcinoma (RCC)–specific survival.

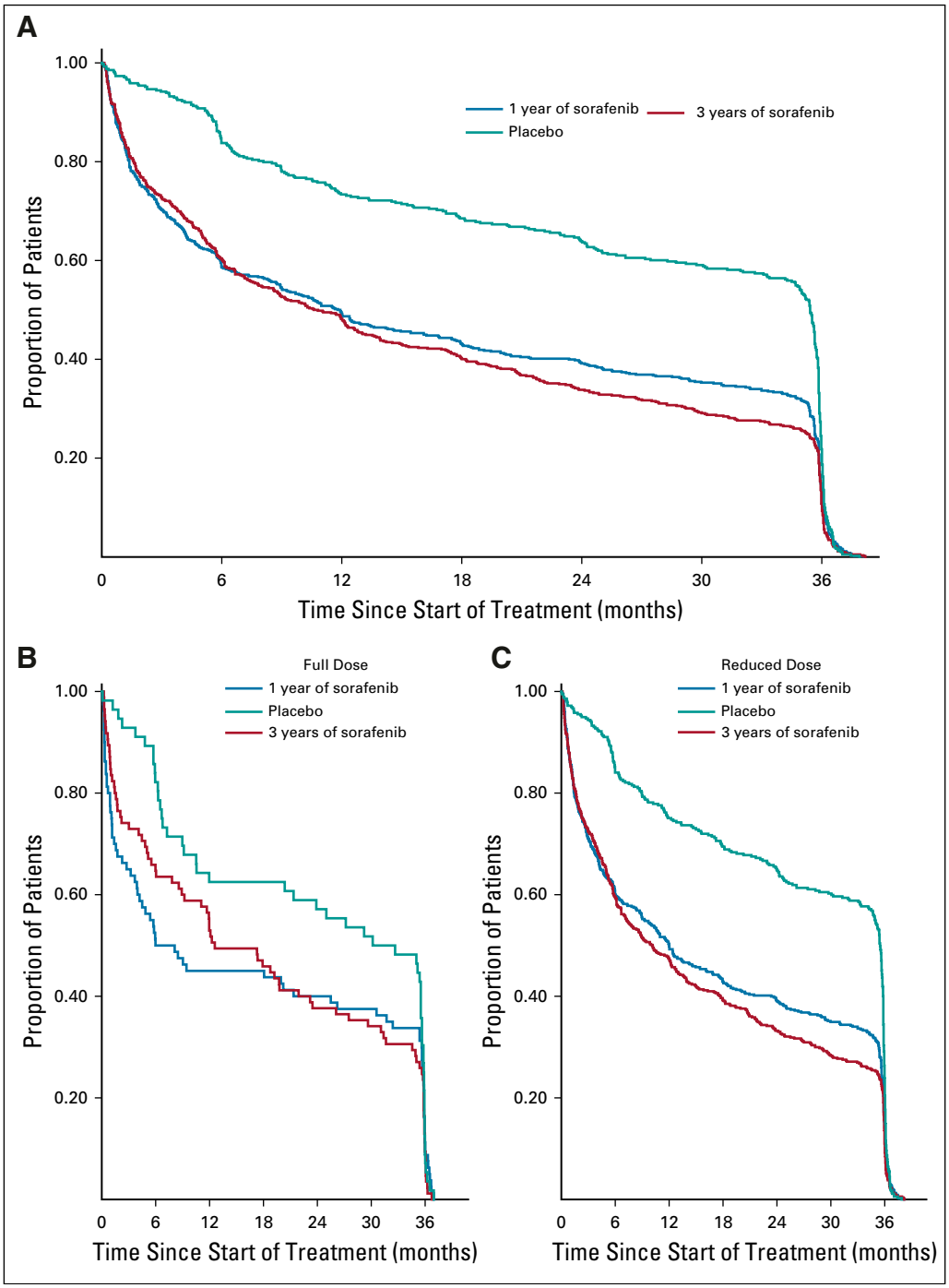

FIG A5. Time to discontinuation or end of treatment by arm, (A) overall and by starting dose: (B) full dose and (C) reduced dose.

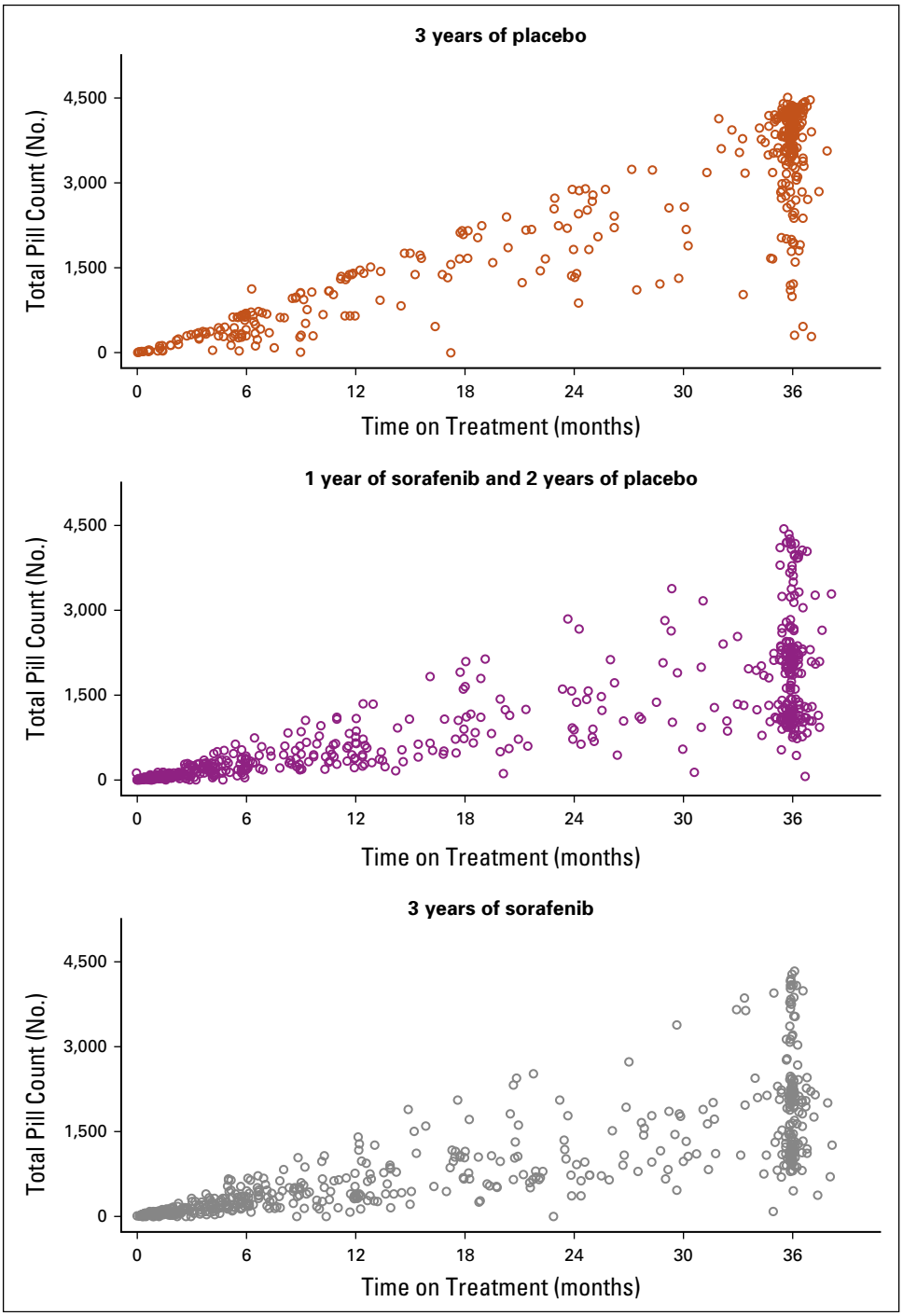

FIG A6. Months on treatment versus total pill count taken per participant in each of the arms. For patients who reached 36 months on treatment, total pill count varied significantly.

TABLE A1. Leibovich Risk Score Components and Risk Group Categories

Feature	Score
Pathologic T category of primary tumor	
pT1a	0
pT1b	2
pT2	3
pT3a-4	4
Regional lymph node status	
pNx or pN0	0
pN1-2	2
Tumor size, cm	
< 10	0
≥ 10	1
Nuclear grade	
1 or 2	0
3	1
4	3
Histologic tumor necrosis	
No	0
Yes	1

NOTE. Leibovich score is the sum of the score given for each feature: low risk, score of 0-2; intermediate risk, score of 3-5; and high risk, score of ≥ 6.

TABLE A2. Summary of Other Causes of Death by Treatment Arm

	No. of Patients		
Cause	Placebo	1 Year of Sorafenib	3 Years of Sorafenib
Cardiovascular	2	5	3
Drug reaction (not trial drug)	1	0	0
Infection	3	6	4
Neurologic disease	0	0	1
Other malignancy	4	9	2
Respiratory	2	0	3
Surgical complication	0	0	1
Trauma	0	0	1
Unknown	5	4	5
Total	17	24	20

TABLE A3. Summary of DFS Results in Leibovich High-Risk Patients, in Patients With Clear Cell RCC, and in the Modified DFS Population

	DFS		RMST		
Comparison	HR (95% CI)	*P*	RMST Estimate Over 10 Years (years; 95% CI)	RMST Difference (years)	*P*
Leibovich high risk, 3 years of sorafenib (n = 295) *v* placebo *v* (n = 206)	1.02 (0.80 to 1.30)	.875	5.37 (4.89 to 5.85) *v* 5.44 (4.85 to 6.03)	−0.07	.86
Leibovich high risk, 1 year of sorafenib (n = 300) *v* placebo (n = 206)	0.92 (0.72 to 1.17)	.49	5.69 (5.23to 6.16) *v* 5.43 (4.85 to 6.01)	0.26	.50
Clear cell RCC, 3 years of sorafenib (n = 550) *v* placebo (n = 361)	0.99 (0.80 to 1.23)	.93	6.83 (6.51 to 7.15) *v* 6.79 (6.40 to 7.19)	0.033	.90
Clear cell RCC, 1 year of sorafenib (n = 534) *v* placebo (n = 361)	0.94 (0.75 to 1.16)	.55	7.01 (6.7 to 7.32) *v* 6.82 (6.42 to 7.22)	0.19	.46

NOTE. In Leibovich high-risk patients, we observed no difference in DFS between patients randomly assigned to 3 years of sorafenib versus placebo or to 1 year of sorafenib versus placebo; nonproportional hazards were observed ($P = .01$ and $P < .0001$, respectively). The RMST estimates over 10 years are shown in the table. In patients with clear cell RCC, we also observed no difference in DFS between patients randomly assigned to 3 years of sorafenib versus placebo or to 1 year of sorafenib versus placebo; nonproportional hazards were observed ($P = .08$ and $P < .0001$, respectively). The RMST estimates over 10 years are shown in the table.

Abbreviations: DFS, disease-free survival; HR, hazard ratio; RCC, renal cell carcinoma; RMST, restricted mean survival time.

TABLE A4. Summary of Modified DFS Results

	Modified DFS[2]		RMST		
Comparison	HR (95% CI)	*P*	RMST Estimate Over 10 Years (years; 95% CI)	RMST Difference (years)	*P*
3 years of sorafenib (n = 639) *v* placebo (n = 430)	1.02 (0.85 to 1.23)	.83	6.43 (6.13 to 6.84) *v* 6.47 (6.11 to 6.84)	0.045	.85
1 year of sorafenib (n = 642) *v* placebo (n = 430)	0.96 (0.80 to 1.15)	.64	6.57 (6.27 to 6.86) *v* 6.44 (6.07 to 6.81)	0.13	.61

NOTE. The following modified definition of DFS was explored to align with the definition used in the ASSURE and S-TRAC trials: time from randomization to first evidence of recurrence, development of any second primary cancer, or death from any cause.

Abbreviations: DFS, disease-free survival; HR, hazard ratio; RMST, restricted mean survival time.

TABLE A5. Metastasis-Free Survival Analysis

	Metastasis-Free Survival		RMST		
Comparison	HR (95% CI)	*P*	RMST Estimate Over 10 Years (years; 95% CI)	RMST Difference (years)	*P*
3 years of sorafenib (n = 639) *v* placebo (n = 430)	1.00 (0.82 to 1.22)	.98	6.89 (6.60 to 7.19) *v* 6.88 (6.52 to 7.24)	0.01	.97
1 year of sorafenib (n = 642) *v* placebo (n = 430)	0.90 (0.74 to 1.10)	.31	7.13 (6.84 to 7.41) *v* 6.86 (6.50 to 7.23)	0.27	.27

Abbreviations: HR, hazard ratio; RMST, restricted mean survival time.

TABLE A6. Renal Cell Carcinoma–Specific Survival Analysis

	Renal Cell Carcinoma–Specific Survival		RMST		
Comparison	HR (95% CI)	*P*	RMST Estimate Over 10 Years (years; 95% CI)	RMST Difference (years)	*P*
3 years of sorafenib (n = 639) *v* placebo (n = 430)	1.12 (0.85 to 1.50)	.42	8.57 (8.35 to 8.79) *v* 8.71 (8.45 to 8.96)	−0.14	.42
1 year of sorafenib (n = 642) *v* placebo (n = 430)	0.91 (0.68 to 1.22)	.52	8.81 (8.61 to 9.02) *v* 8.68 (8.42 to 8.94)	0.13	.44

Abbreviations: HR, hazard ratio; RMST, restricted mean survival time.

TABLE A7. Time on Trial Before Stopping Treatment

	No. of Patients (%)		
Months on Treatment	**Placebo**	**1 Year of Sorafenib Plus 2 Years of Placebo**	**3 Years of Sorafenib**
≤ 1	11 (3)	98 (15)	88 (14)
1-2	8 (2)	58 (9)	55 (9)
2-3	5 (1)	31 (5)	25 (4)
3-6	43 (10)	71 (11)	76 (12)
6-12	43 (10)	59 (9)	74 (12)
12-18	20 (5)	37 (6)	49 (8)
18-24	19 (4)	25 (4)	39 (6)
24-30	20 (5)	24 (4)	29 (5)
30-36+	244 (57)	218 (34)	178 (28)

NOTE. Percentages are based on the number of randomly assigned patients in each arm.

TABLE A8. Time on Treatment

Measure	**Placebo**	**1 Year of Sorafenib**	**3 Years of Sorafenib**
Overall			
Median time on treatment, months (IQR)	35.42 (11.43-35.94)	11.19 (2.00-12.16)	10. 71 (2.27-35.29)
Mean time on treatment, months (SD)	25.63 (13.24)	7.78 (5.21)	16.08 (14.35)
Full dose			
No. of patients	57	84	85
Median time on treatment, months (IQR)	31.41 (6.72-35.86)	5.98 (1.12-12.19)	12.58 (2.20-35.65)
Mean time on treatment, months (SD)	23.31 (14.04)	7.20 (5.56)	17.69 (14.54)
Reduced dose			
No. of patients	373	558	554
Median time on treatment, months (IQR)	35.48 (12.22-35.98)	11.27 (2.30-12.16)	10.15 (2.33-35.19)
Mean time on treatment, months (SD)	25.99 (13.10)	7.86 (5.15)	15.82 (14.32)

Abbreviations: IQR, interquartile range; SD, standard deviation.

TABLE A9. Summary of First Posttrial Treatment

	No. of Patients (%)			
Treatment	**Placebo**	**1 Year of Sorafenib Plus 2 Years of Placebo**	**3 Years of Sorafenib**	**Total**
Sunitinib	34 (8)	54 (8)	64 (10)	152 (9)
Pazopanib	19 (4)	40 (6)	45 (7)	104 (6)
Sorafenib	14 (3)	8 (1)	2 (0.3)	24 (1)
Interferon-α, interleukin-2, fluorouracil	3 (1)	6 (1)	3 (0.5)	12 (0.7)
Other	12 (3)	19 (3)	16 (3)	47 (3)
Total	82 (20)	127 (20)	130 (20)	339 (20)

NOTE. Percentages are based on the number of randomly assigned patients in each arm.

TABLE A10. Characteristics, Inclusion Criteria, and Risk Scores of Completed Adjuvant Trials for Kidney Cancer

Characteristic	ASSURE (ClinicalTrials.gov identifier: NCT00326898)	S-TRAC	PROTECT	ATLAS	SORCE
No. of patients	1,943	615	1,538	724	1,711
Treatment arms	Sunitinib or sorafenib *v* placebo	Sunitinib *v* placebo	Pazopanib *v* placebo	Axitinib *v* placebo	Sorafenib for 1 year or sorafenib for 3 years *v* placebo
Duration of treatment, years	1	1	1	3	3
Inclusion criteria	TNM 2002 staging: pT1b, G3-4, N0 or pNx, M0 pT2, G any, N0 or pNx, M0 pT3, G any, N0 or pNx, M0 pT4, G any, N0 or pNx, M0 pT any, G any, N+ (fully resected), M0	TNM 2002 staging: pT2, G3-4, N0 or pNx, M0 pT3, G any, N0 or pNx, M0 pT4, G any, N0 or pNx, M0 pT any, G any, N+ (fully resected), M0	TNM 2010 staging: pT2, G3-4, N0 or pNx, M0 pT3, G any, N0 or pNx, M0 pT4, G any, N0 or pNx, M0 pT any, G any, N1, M0	TNM 2010 staging: pT2, G any, pN0 or pNx, M0 pT3, G any, pN0 or pNx, M0 pT4, G any, pN0 or pNx, M0 Any pT, G any, pN1, M0	TNM 2002 staging: pT any, N1-2, M0 as per Leibovich score of 3-11 (see Appendix Table A1 for Leibovich score breakdown)
Microscopic disease	M0 patients with evidence of microscopic disease (R1) are acceptable	M0 patients with evidence of microscopic disease (R1) are acceptable		Patients must have no evidence of macroscopic residual disease or metastatic disease	M0 patients with evidence of microscopic disease (R1) are acceptable
Histology	Clear cell and non–clear cell	Clear cell predominant	Clear cell predominant (> 50%)	Clear cell predominant (> 50%)	Clear cell and non–clear cell
Performance status	ECOG 0-1	ECOG 0-2	Karnofsky performance score ≥ 80	ECOG 0-1	ECOG 0-1
Risk score	Modified UISS intermediate high to very high	Modified UISS high risk	SSIGN intermediate to high risk	TNM and Fuhrman grade	Leibovich intermediate to high

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SSIGN, stage, size, grade and necrosis; UISS, University of California Los Angeles Integrated Staging System.