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Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma

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ABSTRACT

BACKGROUND

Cytoreductive nephrectomy has been the standard of care in metastatic renal-cell carcinoma for 20 years, supported by randomized trials and large, retrospective studies. However, the efficacy of targeted therapies has challenged this standard. We assessed the role of nephrectomy in patients with metastatic renal-cell carcinoma who were receiving targeted therapies.

METHODS

In this phase 3 trial, we randomly assigned, in a 1:1 ratio, patients with confirmed metastatic clear-cell renal-cell carcinoma at presentation who were suitable candidates for nephrectomy to undergo nephrectomy and then receive sunitinib (standard therapy) or to receive sunitinib alone. Randomization was stratified according to prognostic risk (intermediate or poor) in the Memorial Sloan Kettering Cancer Center prognostic model. Patients received sunitinib at a dose of 50 mg daily in cycles of 28 days on and 14 days off every 6 weeks. The primary end point was overall survival.

RESULTS

A total of 450 patients were enrolled from September 2009 to September 2017. At this planned interim analysis, the median follow-up was 50.9 months, with 326 deaths observed. The results in the sunitinib-alone group were noninferior to those in the nephrectomy–sunitinib group with regard to overall survival (stratified hazard ratio for death, 0.89; 95% confidence interval, 0.71 to 1.10; upper boundary of the 95% confidence interval for noninferiority, ≤1.20). The median overall survival was 18.4 months in the sunitinib-alone group and 13.9 months in the nephrectomy–sunitinib group. No significant differences in response rate or progression-free survival were observed. Adverse events were as anticipated in each group.

CONCLUSIONS

Sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who were classified as having intermediate-risk or poor-risk disease. (Funded by Assistance Publique–Hôpitaux de Paris and others; CARMENA ClinicalTrials.gov number, NCT00930033.)

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Kidney cancer accounts for 5% of all cancers in men and 3% of all cancers in women, and approximately 15% of these are metastatic at diagnosis.[1] More than 15 years ago, randomized, controlled trials showed prolonged survival with initial nephrectomy, as compared with immunotherapy alone, among patients with metastatic renal-cell cancer,[2,3] and nephrectomy became the standard of care for patients who present with metastatic disease.[4] Early retrospective analyses of prognostic factors that have been associated with survival in patients with metastatic renal-cell carcinoma similarly suggested an overall survival benefit with cytoreductive nephrectomy.[5,6]

Since 2005, the treatment options have rapidly expanded owing to the introduction of therapies targeted to the molecular mechanisms underlying renal-cancer carcinogenesis.[7] Inhibitors of vascular endothelial growth factor (VEGF) signaling, including the VEGF receptor tyrosine kinase inhibitors sunitinib and pazopanib and the anti-VEGF monoclonal antibody bevacizumab, are now standard first-line treatment options for favorable-risk and intermediate-risk metastatic renal-cell carcinoma, whereas the mammalian target of rapamycin (mTOR) inhibitor temsirolimus is widely recommended for patients who have renal-cell carcinoma and poor prognostic risk.[8] Several other agents targeting the VEGF receptor, mTOR, c-MET, or the interaction of the immune checkpoint inhibitor programmed death 1 receptor with its ligand have shown efficacy and are current treatment options for patients with renal-cell carcinoma.[8]

The role of nephrectomy in treating metastatic renal-cell carcinoma in the era of targeted therapy has been brought into question, since there is limited level 1 evidence directly comparing the benefit of nephrectomy with targeted therapy.[9] Multiple retrospective studies have investigated the relative benefits of nephrectomy and targeted therapies, and these have supported a benefit of nephrectomy in patients who receive targeted therapy. A systematic meta-analysis of cohort studies assessing the effect of nephrectomy in patients receiving targeted therapy showed that nephrectomy before targeted therapy was associated with longer overall survival than targeted therapy alone,[10] and a U.S. health database analysis showed that initial nephrectomy was associated with improved survival versus initial targeted therapy.[11]

The Surgery Time (SURTIME) prospective study was designed to investigate the role of initial nephrectomy as compared with deferred nephrectomy and showed longer overall survival with deferred nephrectomy than with initial nephrectomy; however, the study was underpowered for the evaluation of the survival end point because of poor recruitment.[12,13] In the CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques) trial, we aimed to test the benefit of initial nephrectomy followed by targeted therapy in patients with metastatic kidney cancer against the benefits provided by targeted therapy alone.

METHODS

TRIAL OVERSIGHT

The trial was designed under the auspices of the Cancerology Committee of the French Association of Urology and the Urogenital Tumors Study Group and was sponsored by Assistance Publique–Hôpitaux de Paris. The protocol (available with the full text of this article at NEJM.org) was approved by the French National Agency for the Safety of Medicines and Health Products (Agence Nationale de Sécurité du Médicament et des Produits de Santé).

The sponsor and their representatives collected and analyzed the data. All the authors had full access to the trial data. Trial oversight was provided by the first and second authors and by an independent data and safety monitoring board (see the Supplementary Appendix, available at NEJM.org). Sunitinib was purchased at full cost from Pfizer per standard pharmacy practice at each institute. Pfizer was not involved in the design or implementation of the protocol, the analysis of the data, or the preparation or review of the manuscript. Four of the authors wrote the first draft of the manuscript, and medical writing and editorial assistance was funded by the sponsor. All the authors made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and the analyses and for the adherence of the trial to the protocol.

The conduct of the trial conformed with the International Conference on Harmonisation E6

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guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. All the patients provided written informed consent before undergoing any trial procedures.

PATIENTS

Eligible patients were adults (≥18 years of age) with clear-cell renal-cell carcinoma confirmed on mandatory biopsy and documented metastatic disease. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1, an absence of brain metastases or treated brain metastases without recurrence 3 weeks after treatment, and acceptable organ function. ECOG scores range from 0 to 5, with higher numbers indicating greater disability and a score of 5 indicating death. Patients had to be suitable candidates for nephrectomy and eligible for treatment with sunitinib. Patients were assessed by the treating urologist before enrollment regarding the feasibility of primary tumor resection; in cases in which there was doubt regarding feasibility, computed tomographic (CT) scans of the abdomen were referred to the steering committee for a decision. Patients were excluded if they had received previous systemic treatment for kidney cancer (including VEGF-targeted therapy) or anticoagulants or if they had any medical condition, including cardiovascular disease, that ruled them out as candidates for treatment.

TRIAL DESIGN

In this prospective, multicenter, open-label, randomized, phase 3 trial, patients were randomly assigned in a 1:1 ratio to undergo nephrectomy followed by sunitinib treatment or to receive sunitinib alone. Randomization was stratified according to risk group (classified according to the Memorial Sloan Kettering Cancer Center [MSKCC] prognostic model) and center.[5] The MSKCC prognostic factors were a Karnofsky performance status score of less than 80 (on a scale from 0 to 100, with lower scores indicating greater disability), a lactate dehydrogenase level of 1.5 times the upper limit of the normal range, a hemoglobin level that was less than the lower limit of the normal range, a corrected serum calcium level of more than 10 mg per deciliter (2.5 mmol per liter), and a time from diagnosis to treatment of less than 1 year. Patients with one or two prognostic factors were classified as having intermediate-risk disease and those with three or more were classified as having poor-risk disease (Table S1 in the Supplementary Appendix).

Nephrectomy was performed within 28 days after randomization, according to the normal procedures of the institute. In the sunitinib-only group, sunitinib treatment was initiated within 21 days after randomization and was given at an initial dose of 50 mg daily in cycles of 28 days on followed by 14 days off every 6 weeks. In the nephrectomy–sunitinib group, sunitinib treatment was initiated between 3 and 6 weeks after nephrectomy. Dose reductions or interruptions of sunitinib treatment were permitted to manage adverse events. After recruitment and randomization, each patient was followed for a minimum of 2 years.

END POINTS AND ASSESSMENTS

The primary end point was overall survival, which was defined as the time from randomization until death from any cause or until the date of last contact for living patients. Secondary end points included investigator-assessed progression-free survival, the objective response rate, clinical benefit (see below), adherence to treatment, nephrectomy in the sunitinib-only group, postoperative morbidity and mortality, and safety. Progression-free survival was calculated, in months, from the date of randomization to the date of progression or the start date of a second-line treatment. Events in the analysis of progression-free survival included progression in patients undergoing treatment or during follow-up, the start of a new line of treatment, and death from cancer-related causes. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and considered all lesions (target, nontarget, and primary). The objective response rate was defined as the percentage of patients with a complete response or partial response. Clinical benefit was defined as the percentage of patients with a complete response, partial response, or stable disease for more than 12 weeks. Postoperative morbidity was evaluated according to the Clavien–Dindo classification of surgical complications[14] (Table S2 in the Supplementary Appendix), and postoperative mortality was evaluated as the percentage of deaths in the 30 days after nephrectomy. Adverse

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events were evaluated according to the Common Terminology Criteria for Adverse Events, version 3.0, of the National Cancer Institute. Radiographic tumor evaluation (CT scan or magnetic resonance imaging [MRI] of the thorax, abdomen, and pelvis) was performed after every two cycles of sunitinib treatment; CT or MRI scans of the head were performed only if clinically indicated.

STATISTICAL ANALYSIS

To assess the hypothesis that nephrectomy is not necessary in patients presenting with metastatic kidney cancer, we considered that treatment with sunitinib alone from the outset would be considered to be clinically acceptable if the upper boundary of the 95% confidence interval for the hazard ratio for death was 1.20 or less (noninferiority margin). The trial was designed to have 80% power at a one-sided significance level of 5%. To show noninferiority, we planned to enroll 576 patients in order to observe 456 deaths, on the basis of an expected recruitment of 12 patients per month over a period of 48 months. This allowed for two interim analyses — one after the observation of 152 deaths and another after 304 deaths — and for a final analysis to be scheduled either 80 months after the initiation of the trial or 32 months after the enrollment of the last patient. O'Brien–Fleming sequential boundaries were used for decisions regarding early halting of the trial. The second interim analysis after the observation of 326 events at the cutoff date of December 12, 2017, reported here, showed that the O'Brien–Fleming boundary was not reached, so the trial was allowed to continue recruitment. However, in parallel to this second interim analysis, the sponsor made the decision to close the trial early because of slow recruitment, and the steering committee considered the results from this interim analysis sufficient to meet the objectives of the trial.

The rates and 95% confidence intervals for the analyses of overall survival and progression-free survival were estimated by the Kaplan–Meier method in the intention-to-treat population. Tumor response and safety data were analyzed in patients who received sunitinib. Two per-protocol analyses were performed: the first included only patients in the nephrectomy–sunitinib group who had undergone nephrectomy and patients in the sunitinib-alone group who had received sunitinib; and the second included only patients in the nephrectomy–sunitinib group who had undergone nephrectomy and also received sunitinib and patients in the sunitinib-alone group who had received sunitinib.

RESULTS

PATIENTS

Between September 23, 2009, and September 8, 2017, a total of 450 patients were enrolled from 79 centers in France and from other centers in Europe (425 patients from France, 14 from the United Kingdom, 10 from Norway, and 1 from Sweden) (Table S3 in the Supplementary Appendix). Patients were randomly assigned in a 1:1 ratio to undergo nephrectomy and then receive sunitinib treatment (226 patients) or to start treatment with sunitinib alone immediately (224 patients) (Fig. 1). In the nephrectomy–sunitinib group, 16 patients (7.1%) did not undergo nephrectomy and 40 (17.7%) never received sunitinib; in the sunitinib-alone group, 11 patients (4.9%) never received sunitinib and 38 (17.0%) underwent subsequent nephrectomy a median of 11.1 months after randomization for the control of symptoms. Details regarding the nephrectomies are provided in Table S6 in the Supplementary Appendix.

At the time of data cutoff (December 12, 2017), the median follow-up of the patients was 50.9 months overall (95% confidence interval [CI], 44.0 to 56.9; range, 0.0 to 86.6). The majority of patients were men (74.7%), the median age of patients in the intention-to-treat population was 62 years (range, 30 to 87), and 56.0% of the patients overall had an ECOG performance-status score of 0. The demographic and clinical characteristics of the patients at baseline were well balanced between the treatment groups (Table 1). In the nephrectomy–sunitinib group, 55.6% of the patients were in the MSKCC intermediate-risk group and 44.4% were in the poor-risk group; in the sunitinib-alone group, the corresponding values were 58.5% and 41.5%.

Sunitinib treatment was stopped in 67.1% of the patients because of disease progression, in 13.0% because of toxic effects, and in 6.2% because of death. Subsequent anticancer therapies were received by similar percentages of patients

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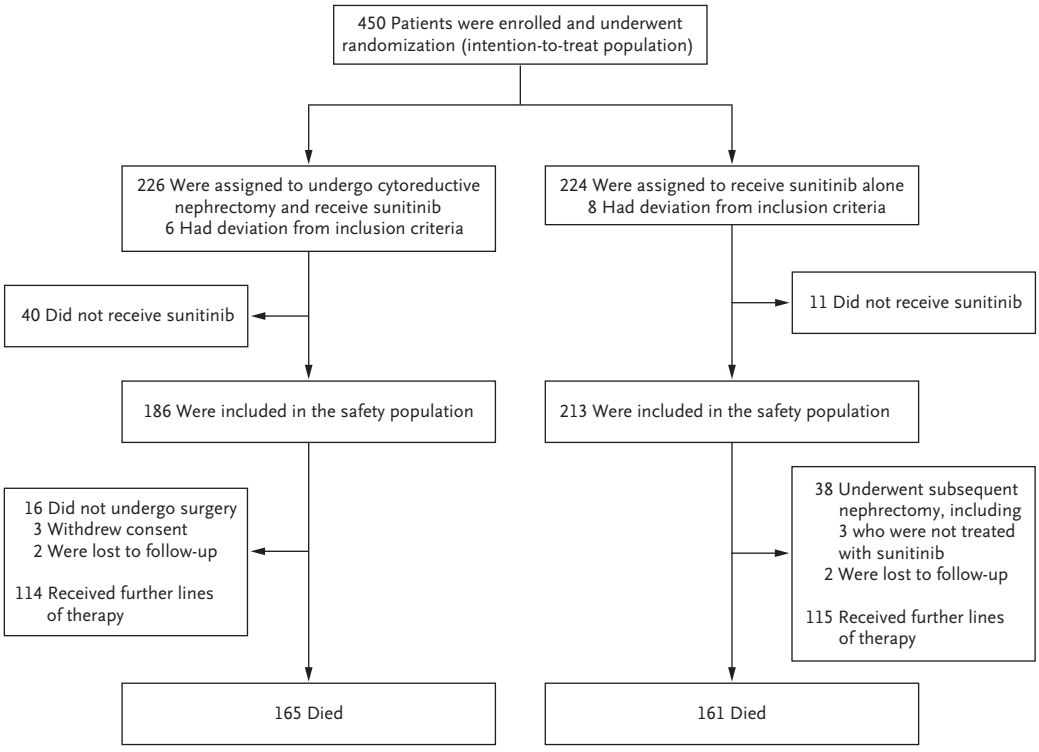

Figure 1. Randomization, Treatment, and Follow-up of the Patients.

The numbers of patients who died were based on the intention-to-treat population. The patients who did not undergo surgery (in the nephrectomy–sunitinib group) or who underwent subsequent nephrectomy (in the sunitinib-alone group), who withdrew consent, who were lost to follow-up, or who received further lines of therapy were all included in the analyses of overall survival and progression-free survival.

in the nephrectomy–sunitinib group and the sunitinib-alone group (50.4% and 51.3%, respectively), the most common being everolimus (in 21.9% and 31.3%) and axitinib (in 23.7% and 25.2%) (Table S7 in the Supplementary Appendix).

EFFICACY

At the time of data cutoff, 326 deaths had occurred, of which 91.0% were cancer-related. In the intention-to-treat population, patients in the sunitinib-alone group had a longer median overall survival than those in the nephrectomy–sunitinib group (18.4 months [95% CI, 14.7 to 23.0] vs. 13.9 months [95% CI, 11.8 to 18.3]) (Fig. 2A). The hazard ratio for death in the analysis of overall survival, stratified according to MSKCC risk score, was 0.89 (95% CI, 0.71 to 1.10). At this planned interim analysis, the upper boundary of the 95% confidence interval for the hazard ratio did not exceed the fixed noninferiority limit (1.20). Thus, sunitinib alone was not inferior to nephrectomy followed by sunitinib. In both the intermediate-risk and poor-risk groups of patients, the median overall survival was longer in the sunitinib-alone group than in the nephrectomy–sunitinib group (23.4 vs. 19.0 months in the intermediate-risk subgroup and 13.3 vs. 10.2 months in the poor-risk group). In the intermediate-risk population, the hazard ratio for death in the sunitinib-alone group, as compared with the nephrectomy–sunitinib group, was 0.92 (95% CI, 0.68 to 1.24), and in the poor-risk population, the hazard ratio was 0.86 (95% CI, 0.62 to 1.17).

At the time of data cutoff, 390 events had been observed for the analysis of progression-free survival; 86.7% of the events were disease progression, death from disease progression, or the start of a new line of treatment. Although

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Nephrectomy–Sunitinib (N=226)	Sunitinib Alone (N=224)
Median age (range) — yr	63 (33–84)	62 (30–87)
Male sex — no. (%)	169 (74.8)	167 (74.6)
MSKCC risk category — no./total no. (%)†		
Intermediate risk	125/225 (55.6)	131/224 (58.5)
Poor risk	100/225 (44.4)	93/224 (41.5)
ECOG performance-status score — no. (%)‡		
0	130 (57.5)	122 (54.5)
1	96 (42.5)	102 (45.5)
Fuhrman grade of renal-cell carcinoma — no./total no. (%)§		
1 or 2	77/150 (51.3)	82/156 (52.6)
3 or 4	73/150 (48.7)	74/156 (47.4)
Tumor–node–metastasis stage — no./total no. (%)¶	71/207 (34.3)	50/194 (25.8)
Tumor stage		
T1	5/67 (7.5)	7/49 (14.3)
T2	13/67 (19.4)	13/49 (26.5)
T3 or 4	47/67 (70.1)	25/49 (51.0)
Tx	2/67 (3.0)	4/49 (8.2)
Node stage		
N0	23/66 (34.8)	18/49 (36.7)
N1	13/66 (19.7)	6/49 (12.2)
N2	7/66 (10.6)	13/49 (26.5)
Nx	23/66 (34.8)	12/49 (24.5)
Median primary tumor size (range) — mm	88 (6–200)	86 (12–190)
Median no. of metastatic sites (range)	2 (1–5)	2 (1–5)
Median tumor burden (range) — mm‖	140 (23–399)	144 (39–313)
Location of metastases — no./total no. (%)		
Lung	172/217 (79.3)	161/221 (72.9)
Bone	78/217 (35.9)	82/221 (37.1)
Lymph nodes	76/217 (35.0)	86/221 (38.9)
Other	78/217 (35.9)	90/221 (40.7)

* The characteristics of the patients at baseline were well balanced between the treatment groups.
† The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic factors regarding risk were: a Karnofsky performance-status score of less than 80 (on a scale from 0 to 100, with lower scores indicating greater disability), a lactate dehydrogenase level of 1.5 times the upper limit of the normal range, a hemoglobin level that was less than the lower limit of the normal range, a corrected serum calcium level of more than 10 mg per deciliter (2.5 mmol per liter), and a time from diagnosis to treatment of less than 1 year. Patients with one or two prognostic factors were classified as having intermediate-risk disease and those with three or more were classified as having poor-risk disease.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability and a score of 5 indicating death.
§ The Fuhrman grade of renal-cell carcinoma is assessed on a scale of 1 to 4, with grade 1 indicating the least atypia and grade 4 the most.
¶ The tumor–node–metastasis stage was determined according to the criteria of the Union for International Cancer Control TNM Classification of Malignant Tumours.[15] Metastasis was an eligibility criterion in all patients.
‖ Tumor burden was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1.

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radiographic imaging of tumors was not mandatory before the initiation of sunitinib in the nephrectomy–sunitinib group, 223 patients had radiographic imaging data of target lesions at baseline, and of the 176 patients who received sunitinib, 111 had radiographic imaging of the target lesion performed at treatment initiation. In the sunitinib-alone group, 222 of 223 patients with data (99.6%) had a CT or MRI scan at baseline, before the initiation of sunitinib alone. The median progression-free survival was longer among patients in the sunitinib-alone group than among those in the nephrectomy–sunitinib group (8.3 months [95% CI, 6.2 to 9.9] vs. 7.2 months [95% CI, 6.7 to 8.5]) (Fig. 2B). The hazard ratio for progression or death, stratified according to risk group, was 0.82 (95% CI, 0.67 to 1.00). The results of the per-protocol analyses were consistent with those of the intention-to-treat analysis (Tables S4 and S5 in the Supplementary Appendix).

The objective response rate was similar in the two trial groups (29.1% in the sunitinib-alone group and 27.4% in the nephrectomy–sunitinib group) (Table 2), although the rate of disease control was nonsignificantly higher in the sunitinib-alone group than in the nephrectomy–sunitinib group (74.6% vs. 61.8%) (Table 2). Clinical benefit was observed in 47.9% of the patients in the sunitinib-alone group, as compared with 36.6% of those in the nephrectomy–sunitinib group (P=0.02) (Table 2).

Postoperative death in the month after nephrectomy was recorded in 4 patients in the nephrectomy–sunitinib group. Among patients with postoperative complications in the nephrectomy–sunitinib group (82 of 210 patients), complications of Clavien–Dindo grade III or higher occurred in 15.9% (13 of 82 patients).

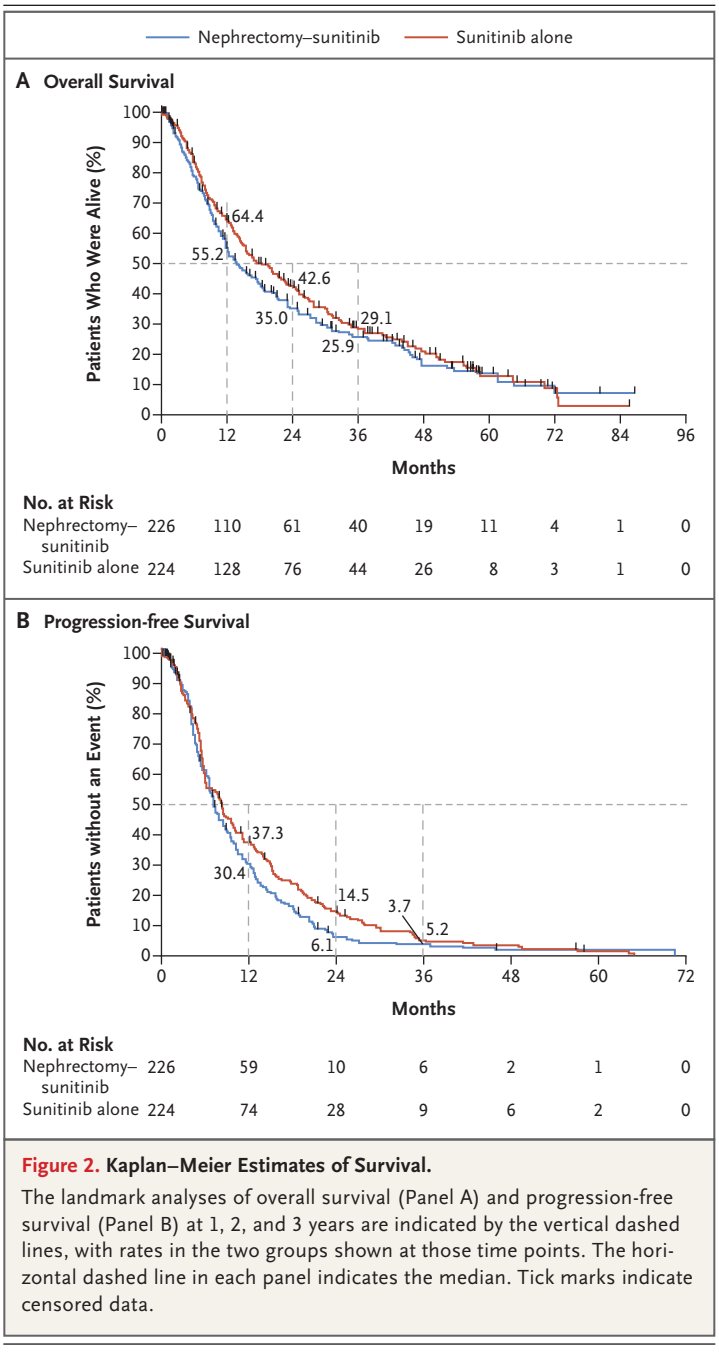

Figure 2. Kaplan–Meier Estimates of Survival.

The landmark analyses of overall survival (Panel A) and progression-free survival (Panel B) at 1, 2, and 3 years are indicated by the vertical dashed lines, with rates in the two groups shown at those time points. The horizontal dashed line in each panel indicates the median. Tick marks indicate censored data.

EXPOSURE AND SAFETY

The median duration of sunitinib treatment was 6.7 months (range, 1.4 to 67.2) in the nephrectomy–sunitinib group and 8.5 months (range, 0.9 to 63.7) in the sunitinib-alone group (P=0.04). Dose reduction occurred in 57 of 186 patients (30.6%) in the nephrectomy–sunitinib group and in 65 of 213 (30.5%) in the sunitinib-alone group. The majority of dose reductions were done to manage adverse events.

Only severe (grade 3 or 4) adverse events are reported in this article because the safety profile of sunitinib is well established. Overall, 38.1% of the patients had an adverse event of grade 3 or 4; a total of 61 patients (32.8%) in the nephrectomy–sunitinib group and 91 (42.7%) in the sunitinib-alone group reported adverse events of grade 3

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Table 2. Tumor Response Outcomes.*

Response	Nephrectomy–Sunitinib (N=186)	Sunitinib Alone (N=213)
Best overall response — no./total no. (%)		
Complete response	1/178 (0.6)	0/208
Partial response	50/178 (28.1)	62/208 (29.8)
Stable disease	64/178 (36.0)	97/208 (46.6)
Progression of disease	49/178 (27.5)	40/208 (19.2)
Could not be evaluated	14/178 (7.9)	9/208 (4.3)
Objective response rate — % (95% CI)†	27.4 (21.1–34.4)	29.1 (23.1–35.7)
Disease control rate — % (95% CI)‡	61.8 (54.4–68.8)	74.6 (68.2–80.3)
Clinical benefit — no. (%)§	68 (36.6)	102 (47.9)

* Tumor response was analyzed in patients who received sunitinib. Some patients could not be evaluated for tumor response because of adverse events during treatment or deterioration of condition.
† Objective response was defined as a complete or partial response.
‡ Disease control was defined as a complete or partial response or stable disease.
§ Clinical benefit was defined as disease control beyond 12 weeks (P=0.02 for this comparison).

or 4 (P=0.04) (Table 3). The most common adverse events of grade 3 or 4 that were observed in the 152 patients in the safety population (i.e., patients treated with sunitinib) who reported an adverse event of grade 3 or 4 were asthenia (in 37 patients), the hand–foot syndrome (in 20), anemia (in 16), and neutropenia (in 15). Grade 3 or 4 renal or urinary tract disorders occurred in 1 patient in the nephrectomy–sunitinib group and in 9 in the sunitinib-alone group (P=0.051). For all other toxic effects, no significant difference was evident between the trial groups.

DISCUSSION

Nephrectomy is currently recommended in patients with a good performance status and large primary tumors with limited volumes of metastatic disease and is not recommended in patients with poor performance status,[4] but there has been limited level 1 evidence to support the use of nephrectomy in the context of targeted therapy. Given the many approved options for systemic targeted therapy that are now available, the reassessment of the role of surgery in disease management is important. This trial showed that sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who had been classified as having MSKCC intermediate-risk or poor-risk disease.

These findings contrast with those of previous retrospective and database studies, which suggested an overall survival benefit with nephrectomy in patients treated with targeted therapies.[10,11,16] Retrospective analyses such as these are subject to selection bias; patients who are selected for nephrectomy are more likely to have more favorable clinical characteristics, such as good performance status and limited metastatic volume, than those who are not selected for surgery, a factor that potentially contributes to survival differences. Data from a large, retrospective study by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) showed that patients undergoing nephrectomy had better prognostic profiles than patients whose diseased kidney was not removed and that prognostic factors modified the effect of the operation on survival.[17] Patients with multiple risk factors did not have a survival benefit with nephrectomy.[10] In a National Cancer Database analysis involving 4223 patients with metastatic renal-cell carcinoma who were treated with nephrectomy and targeted therapy, overall survival rates were significantly lower among patients who underwent nephrectomy before targeted therapy than among those who underwent nephrectomy after targeted therapy.[16] However, analyses of hospital registries such as these are subject to selection bias regarding how clinicians opted to administer targeted therapy (before or after nephrectomy).

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Table 3. Summary of Severe Adverse Events in Sunitinib-Treated Patients.*

Event	Nephrectomy–Sunitinib (N=186)	Sunitinib Alone (N=213)
	no. of patients (%)	
Any adverse event of grade 3 or 4†	61 (32.8)	91 (42.7)
Asthenia	16 (8.6)	21 (9.9)
Inflammation of mucosa	1 (0.5)	6 (2.8)
Edema	0	4 (1.9)
Neutropenia	5 (2.7)	10 (4.7)
Thrombocytopenia	7 (3.8)	5 (2.3)
Anemia	5 (2.7)	11 (5.2)
Hand–foot syndrome	8 (4.3)	12 (5.6)
Intratumoral hemorrhage	0	1 (0.5)
Pulmonary embolism	2 (1.1)	2 (0.9)
Severe high blood pressure	6 (3.2)	7 (3.3)
Left ventricular failure	0	1 (0.5)
Heart failure	0	1 (0.5)
Hepatitis	1 (0.5)	1 (0.5)
Liver failure	0	2 (0.9)
Severe hypothyroidism	3 (1.6)	1 (0.5)
Musculoskeletal or systemic disorder	2 (1.1)	5 (2.3)
Respiratory, thoracic, or mediastinal disorder	3 (1.6)	4 (1.9)
Renal or urinary tract disorder‡	1 (0.5)	9 (4.2)
Gastrointestinal perforation	1 (0.5)	2 (0.9)
Seizure or convulsions	0	1 (0.5)
Other	34 (18.3)	47 (22.1)

* Shown are adverse events of grade 3 or 4 that were observed among patients who received sunitinib.
† P=0.04.
‡ P=0.051.

Avoiding surgery can provide other benefits for patients. Initial nephrectomy can delay the start of systemic targeted therapies that have shown a survival benefit, and patients may die before receiving such therapies.[18] Avoiding nephrectomy also avoids surgical complications involving blood transfusions, further operations, or intensive care, which may also delay systemic therapy.[19] In addition, there is uncertainty about which patients are appropriate candidates for nephrectomy.[8]

A potential limitation of this trial is that enrolled patients were appropriate candidates for nephrectomy in the opinion of the treating urologist; therefore, the results are not generally applicable to patients with a poor performance status, minimal primary tumor burden, and high volumes of metastatic disease, because these patients are not generally recommended to undergo nephrectomy.[4] The use of MSKCC risk groups, which were the risk groups in common use at the time the trial was launched, is an unavoidable limitation of this analysis, since these are not as relevant as IMDC risk groups in the era of targeted therapy. In addition, the inclusion of patients with minimal tumor burden could have resulted in different survival outcomes. Because this was a noninferiority trial, the results may underestimate the benefit of nephrectomy. Another limitation of this trial is the recruitment of

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fewer patients than planned (450 patients rather than 576), which reduced the statistical power. However, the trend in longer overall survival and progression-free survival among patients who did not undergo nephrectomy suggests that our conclusion is correct. Finally, the exclusion, at the investigator's discretion, of patients with low metastatic burden could be considered to result in a potential bias, and this situation may have contributed to the high proportion of patients with features indicating poor prognostic risk and the relatively short overall survival that was observed in the trial. These patients are usually considered to be good candidates for nephrectomy followed by surveillance.

Sunitinib was the therapy chosen in the design of CARMENA on the basis of supporting evidence that was available at the time. Although sunitinib and pazopanib are currently the most commonly used treatments in patients with metastatic renal-cell carcinoma with a good or intermediate prognosis,[4] two recent randomized trials involving patients with an intermediate or poor prognosis showed the superiority of the c-MET inhibitor cabozantinib[20] and immune checkpoint inhibitor combination therapy (nivolumab plus ipilimumab)[21] over sunitinib. These agents will probably be incorporated as initial treatment options for patients with intermediate-risk or poor-risk disease. Our trial included patients with disease features indicating poor risk, and the findings confirm current treatment guideline recommendations for systemic targeted therapy in patients with poor-risk metastatic renal-cell carcinoma.

Although nephrectomy may have a role in controlling symptoms in some patients with metastatic renal-cell carcinoma, as suggested by retrospective studies,[11,17] there is no "one size fits all" approach. The multimodal approach of individualized treatment provides appropriate management of metastatic renal-cell carcinoma. Data are lacking regarding the role of nephrectomy before immune-checkpoint inhibitors in patients with renal-cell carcinoma.

In conclusion, in this trial, sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who were in the MSKCC intermediate-risk or poor-risk groups.

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APPENDIX

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.

2. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med 2001;345:1655-9.

3. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 2001;358:966-70.

4. Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:Suppl 5:v58-v68.

5. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530-40.

6. Neves RJ, Zincke H, Taylor WF. Metastatic renal cell cancer and radical nephrectomy: identification of prognostic factors and patient survival. J Urol 1988;139:1173-6.

7. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. N Engl J Med 2017;376:354-66.

8. Bamias A, Escudier B, Sternberg CN, et al. Current clinical practice guidelines for the treatment of renal cell carcinoma: a systematic review and critical evaluation. Oncologist 2017;22:667-79.

9. Culp SH. Cytoreductive nephrectomy and its role in the present-day period of targeted therapy. Ther Adv Urol 2015;7:275-85.

10. García-Perdomo HA, Zapata-Copete JA, Castillo-Cobaleda DF. Role of cytoreductive nephrectomy in the targeted therapy era: a systematic review and meta-analysis. Investig Clin Urol 2018;59:2-9.

11. Bhindi B, Habermann EB, Mason RJ, et al. Comparative survival following initial cytoreductive nephrectomy versus initial targeted therapy for metastatic renal cell carcinoma. J Urol 2018 March 21 (Epub ahead of print).

12. Stewart GD, Aitchison M, Bex A, et al. Cytoreductive nephrectomy in the tyrosine kinase inhibitor era: a question that may never be answered. Eur Urol 2017;71:845-7.

13. Bex A, Mulders P, Jewett MAS, et al. Immediate versus deferred cytoreductive nephrectomy (CN) in patients with synchronous metastatic renal cell carcinoma (mRCC) receiving sunitinib (EORTC 30073 SURTIME). Eur Urol Suppl 2018;17:(2):e1-e2. abstract.

14. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery 1992;111:518-26.

15. Sobin LH, Gospodarowicz MK, Wittekind C, eds. International Union against Cancer (UICC) TNM classification of malignant tumours. 7th ed. Oxford, United Kingdom: Wiley-Blackwell, 2009.

16. Hanna N, Sun M, Meyer CP, et al. Survival analyses of patients with metastatic renal cancer treated with targeted therapy with or without cytoreductive nephrectomy: a National Cancer Data Base study. J Clin Oncol 2016;34:3267-75.

17. Heng DY, Wells JC, Rini BI, et al. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur Urol 2014;66:704-10.

18. Bhindi B, Habermann E, Mason R, et al. Survival following upfront cytoreductive nephrectomy versus targeted therapy for metastatic renal cell carcinoma. J Clin Oncol 2018;36:Suppl:672. abstract.

19. Silberstein JL, Adamy A, Maschino AC, et al. Systematic classification and prediction of complications after nephrectomy in patients with metastatic renal cell carcinoma (RCC). BJU Int 2012;110:1276-82.

20. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN Trial. J Clin Oncol 2017;35:591-7.

21. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277-90.

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