JAMA Oncology | Original Investigation

Alternating Treatment With Pazopanib and Everolimus vs Continuous Pazopanib to Delay Disease Progression in Patients With Metastatic Clear Cell Renal Cell Cancer
The ROPETAR Randomized Clinical Trial

Geert A. Cirkel, MD; Paul Hamberg, MD, PhD; Stefan Sleijfer, MD, PhD; Olaf J. L. Loosveld, MD; M. Wouter Dercksen, MD, PhD; Maartje Los, MD, PhD; Marco B. Polee, MD, PhD; Franchette van den Berkmortel, MD, PhD; Maureen J. Aarts, MD, PhD; Laurens V. Beerepoot, MD, PhD; Gerard Groenewegen, MD, PhD; Martijn P. Lolkema, MD, PhD; Metin Tascilar, MD, PhD; Johanna E. A. Portielje, MD, PhD; Frank P. J. Peters, MD, PhD; Heinz-Josef Klümpen, MD, PhD; Vincent van der Noort, PhD; John B. A. G. Haanen, MD, PhD; Emile E. Voest, MD, PhD; for the Dutch WIN-O Consortium

IMPORTANCE To our knowledge, this is the first randomized clinical trial evaluating an alternating treatment regimen in an attempt to delay disease progression in clear cell renal cell carcinoma.

OBJECTIVE To test our hypothesis that an 8-week rotating treatment schedule with pazopanib and everolimus delays disease progression, exhibits more favorable toxic effects, and improves quality of life when compared with continuous treatment with pazopanib.

DESIGN, SETTING, AND PARTICIPANTS This was an open-label, randomized (1:1) study (ROPETAR trial). In total, 101 patients with treatment-naive progressive metastatic clear cell renal cell carcinoma were enrolled between September 2012 and April 2014 from 17 large peripheral or academic hospitals in The Netherlands and followed for at least one year.

INTERVENTIONS First-line treatment consisted of either an 8-week alternating treatment schedule of pazopanib 800 mg/d and everolimus 10 mg/d (rotating arm) or continuous pazopanib 800 mg/d (control arm) until progression. After progression, patients made a final rotation to either pazopanib or everolimus monotherapy (rotating arm) or initiated everolimus (control arm).

MAIN OUTCOME AND MEASURES The primary end point was survival until first progression or death. Secondary end points included time to second progression or death, toxic effects, and quality of life.

RESULTS A total of 52 patients were randomized to the rotating arm (median [range] age, 65 [44-87] years) and 49 patients to the control arm (median [range] age, 67 [38-82] years). Memorial Sloan Kettering Cancer Center risk category was favorable in 26% of patients, intermediate in 58%, and poor in 15%. Baseline characteristics and risk categories were well balanced between arms. One-year PFS1 for rotating treatment was 45% (95% CI, 33-60) and 32% (95% CI, 21-49) for pazopanib (control). Median time until first progression or death for rotating treatment was 7.4 months (95% CI, 5.6-18.4) and 9.4 months (95% CI, 6.6-11.9) for pazopanib (control) (P = .37). Mucositis, anorexia, and dizziness were more prevalent in the rotating arm during first-line treatment. No difference in quality of life was observed.

CONCLUSIONS AND RELEVANCE Rotating treatment did not result in prolonged progression-free-survival, fewer toxic effects, or improved quality of life. First-line treatment with a vascular endothelial growth factor inhibitor remains the optimal approach in metastatic clear cell renal cell carcinoma.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01408004

JAMA Oncol. 2017;3(4):501-508. doi:10.1001/jamaoncol.2016.5202
Published online December 1, 2016.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the Dutch WIN-O Consortium are listed at the end of the article.

Corresponding Author: Emile E. Voest, MD, PhD, Netherlands Cancer Institute, Plesmanlaan 121, PO Box: 90203, 1006 BE Amsterdam, The Netherlands (e.voest@nki.nl).

An estimated 338 000 patients are diagnosed with renal cell carcinoma (RCC) yearly worldwide, and incidence is rising.[1,2] In developed countries, approximately 30% to 50% of patients initially presenting with nonmetastatic disease develop distant metastases, while 30% of patients present with metastatic disease at diagnosis.[3,4] For patients with advanced disease, current guidelines recommend first-line treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKI) followed by mammalian target of rapamycine (mTOR) inhibitors or a different VEGFR-TKI in second-line setting for patients with good or intermediate prognosis RCC.[5] A serious limitation of these drugs is the development of resistance eventually leading to progression. Median progression-free survival (PFS) is on average 9 months when treated with a VEGFR-TKI in first-line and 4 months when treated with an mTOR inhibitor in second-line.[6-9]

Interestingly, resistance to VEGFR-TKI is reversible in a substantial number of patients after drug withdrawal.[10-12] The mechanism of this reversible resistance is incompletely understood but several mechanisms have been proposed. These include nonmutational epigenetic alterations,[13,14] treatment-induced shift in clonal homeostasis that can be restored by treatment interruption,[15-17] and lysosomal sequestration of VEGFR-TKI.[18] These preclinical and clinical findings provide a rationale to prospectively explore an alternating treatment regimen in patients with metastatic RCC to delay the development of resistance and maximize utilization of approved drugs. Recent findings by Dos Santos et al[19] provide further support for this rationale. Nude mice were inoculated with Caki-1 renal cancer cells and treated with a 1-, 2-, or 3-week alternating treatment schedule of sunitinib and everolimus. All 3 alternating treatment schedules resulted in prolonged median time to progression when compared with everolimus of sunitinib monotherapy. In contrast to data from clinical trials in humans, median PFS on everolimus monotherapy appeared superior when compared with sunitinib monotherapy in this model.[6,20,21]

In addition, rotating 2 classes of drugs with proven efficacy may also have a favorable effect on treatment tolerability. Vascular endothelial growth factor receptor TKIs and mTOR inhibitors are associated with significant toxic effects leading to treatment discontinuation in 20% to 24% of patients receiving VEGFR-TKIs and in approximately 14% of patients receiving mTOR inhibitors.[6,20-22] Alternating 2 different agents with only partially overlapping toxic effect profiles and targeting different pathways may allow patients to recover from incurred toxic effects while being treated with another active agent. This may lead to improved quality of life (QoL) and treatment compliance.

To test the hypothesis that alternating treatment delays the development of resistance and exhibits more favorable toxic effects, we embarked on an open-label, randomized phase 2 study comparing an 8-week alternating schedule of pazopanib and everolimus with standard of care sequential treatment with these agents.

Key Points

Question For patients with metastatic clear cell renal cell cancer, does rotating treatment with pazopanib and everolimus result in delayed resistance, fewer toxic effects, and improved quality of life when compared with sequential treatment with pazopanib and everolimus?

Findings In this clinical trial, 101 patients with clear cell renal cell carcinoma were randomized to a group receiving rotating treatment with pazopanib and everolimus or pazopanib monotherapy. Median progression-free survival was 7.4 months with rotating treatment and 9.4 months with pazopanib monotherapy, and rotating treatments did not result in fewer toxic effects or improved quality of life.

Meaning First-line treatment with single-agent vascular endothelial growth factor inhibitor until progression remains the first choice in first-line setting of metastatic clear cell renal cell cancer.

Methods

Patient Selection

Patients 18 years or older with systemic treatment-naive, histologically confirmed, locally advanced or metastatic clear cell renal cell carcinoma (ccRCC) were eligible. Additional inclusion criteria included measurable disease according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1,[23] Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and adequate organ function. Main exclusion criteria included a prior malignancy, history or clinical evidence of central nervous system metastases or leptomeningeal disease, presence of uncontrolled infection, poorly controlled hypertension, history of cerebrovascular accident including transient ischemic attack, pulmonary embolism or untreated deep venous thrombosis within the past 6 months, or any condition which potentially might interfere with the patients safety or compliance to study procedures.

Trial protocol is available as Supplement 1.

Study Design

The ROPETAR study was performed as a multicenter, open-label, randomized phase 2 trial.

Patients were stratified according to the Memorial Sloan Kettering Cancer Center (MSKCC) risk categories (favorable vs intermediate vs poor risk, based on Karnofsky performance status <80%, hemoglobin level below the lower limit of normal, corrected serum calcium >10 mg/dL, lactate dehydrogenase >1.5 times upper limit of normal, and time from initial diagnosis <1 year before randomization).[20,24] Randomization (1:1) was performed by using a computerized randomization program (ALEA Randomization Service), allocating patients to the rotating or control arm. In the rotating arm, patients received continuous rotating treatment with 8 weeks of pazopanib 800 mg/d followed by 8 weeks of everolimus 10 mg/d until disease progression (PD) according RECIST 1.1. After PD, patients made a final rotation to either pazopanib or everolimus continuous monotherapy. In this study 1 cycle was defined as

8 weeks of treatment. In the control arm patients received first-line treatment with pazopanib 800 mg/d until PD, at which point pazopanib was immediately followed by everolimus 10 mg/d as second-line treatment (eFigure 1 in Supplement 2). Drug-dose interruptions or modifications were allowed according to standard clinical practice. Primary end point was progression-free survival 1 (PFS1) defined as time between randomization and first PD or death. Secondary end points included PFS2, defined as time between randomization and second PD or death, toxic effects, and overall survival (OS). Furthermore time to second progression(PFS2II), defined as time between first PD and second PD (or death) on everolimus or pazopanib monotherapy as second-line treatment in the rotating arm or on everolimus in the control arm, was adopted as secondary end point. Additionally, effect on QoL was compared between arms as secondary objective.

The study was approved by the ethics committee of the University Medical Center Utrecht and was conducted in adherence to the most recent Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Assessments

Safety

Clinical assessments for safety, including vital signs, World Health Organization (WHO) performance status, toxic effects, and concomitant medication were evaluated at baseline and biweekly during the first period of 16 weeks and every 4 weeks thereafter. Laboratory evaluations (urine analysis and blood chemistry and hematology) were performed at baseline, day 15, day 29, and every 4 weeks thereafter. Toxic effects were assessed by the treating physician at every visit throughout the study course according to the National Institutes of Health National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Quality of Life

Quality of life was measured throughout the study course by using both The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 version 3.0 (EORTC QLQ-C30) and Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease-Related Symptoms (FKSI-DRS) questionnaire.[25,26] The FKSI-DRS specifically addresses 9 disease-related symptoms often observed in patients with renal cancer. The EORTC QLQ-C30 covers 5 functional scales (Physical, Role, Emotional, Cognitive, and Social), 3 symptom scales (fatigue, pain, nausea, and vomiting), and a global health status or QoL scale. Quality of life was measured at baseline followed by measurements every 8 weeks thereafter. An additional measurement was performed at the end-of-treatment visit.

Efficacy

Response evaluation was performed using computed tomography or magnetic resonance imaging and was performed at baseline and every 8 weeks thereafter until PD according to RECIST 1.1.[23] Survival information on all patients, including initiation of new anticancer therapies, after the patient's end-of-treatment visit was collected every 8 weeks up to 1 year after the last patient was randomized.

Statistical Methods

A total sample size of 100 patients was planned. From literature it was estimated that the 1-year PFS1 in the control arm would be 50%. An increase from 50% to 80% 1-year PFS of the rotating schedule over standard of care with first-line VEGFR-TKI was considered to be clinically relevant. Primary analysis was planned when over 60 events (first progression or death) were recorded, enabling detection of an increase in 1-year PFS to 80% (power 90%, $\alpha = .05$, 2-tailed test).

Progression-free survival and OS curves were constructed by means of the Kaplan-Meier technique and analyzed according to the intention-to-treat principle using stratified and unstratified Cox regression and log-rank tests. In all cases the stratified statistics were stratified by MSKCC risk categories. Patients who had not died or experienced progression at the time of analysis were censored at the time of their last tumor measurement. Patients who received further off-study anticancer therapy were censored at their last tumor measurement before start of a new anticancer therapy. Adverse events (AE) were summarized descriptively and were assessed in patients who received at least 1 drug dose. Occurrence of common AEs and of serious AEs was compared between arms using Fisher exact test. Main QoL outcome measurements (FKSI-DRS symptom scale, Physical Functioning and QoL according to QLQ-C30) were summarized and plotted over time for both arms. Additionally, time to first and definitive 20% deterioration in QoL scales compared with baseline was plotted as Kaplan-Meier curves and compared using a log-rank test. Interim safety and efficacy analyses were performed after 20 and 40 events by an independent Data Safety Monitoring Board in adherence to DAMOCLES guidelines.[27] Differences in PFS between the rotating and control arms were assessed using log-rank tests with a significance level defined by the O'Brien-Fleming approach for 3 looks.[28]

Results

Patients

Between September 2012 and April 2014, 52 and 49 patients were randomized to the rotating and control arms, respectively, in 15 participating hospitals in the Netherlands. Baseline characteristics, including MSKCC risk categories, were well balanced and are shown in the **Table**. Individual baseline MSKCC factors and additional International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic factors[29] are provided in eTable 1 in Supplement 2. Discrepancies between data entered at time of randomization by the treating physician and postrandomization MSKCC risk assessment by independent data managers resulted in more patients with a Karnofsky performance score lower than 80% in the control arm (control: 7 [14%] vs rotating: 0; $P < .005$). A prior nephrectomy was performed in 25 patients (51%) in the control arm vs 17 patients (33%) in the rotating arm ($P = .07$). All 101 patients were included in our efficacy analysis. The safety

Table. Baseline Characteristics

Variable	No. (%) All Patients (n = 101)	Rotating Arm (n = 52)	Control Arm (n = 49)
Sex			
Male	69 (68)	38 (73)	31 (63)
Female	32 (32)	14 (27)	18 (37)
Age, median (range), y	66 (38-87)	65 (44-87)	67 (38-82)
ECOG PS			
0	57 (56)	31 (60)	26 (53)
1	39 (39)	19 (36)	20 (41)
2	4 (4)	2 (4)	2 (4)
Missing	1 (1)	0 (0)	1 (2)
MSKCC risk score			
Favorable	26 (26)	14 (27)	12 (24)
Intermediate	59 (58)	32 (62)	27 (55)
Poor	15 (15)	6 (12)	9 (18)
NA	1 (1)	0 (0)	1 (2)
Metastatic sites			
Lung	69 (68)	35 (67)	34 (69)
Liver	11 (11)	6 (12)	5 (10)
Lymph nodes	39 (39)	21 (40)	18 (37)
Bone	35 (35)	16 (31)	19 (39)
Brain	1 (1)	1 (2)	0 (0)
Prior nephrectomy	42 (42)	17 (33)	25 (51)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MSKCC, Memorial Sloan Kettering Cancer Center, categories based on postrandomization data assessment; NA, not available.

population consisted of 100 patients who received at least 1 dose of study treatment. At time of analysis 20 patients (39%) in the rotating arm and 20 patients (41%) in the control arm initiated second-line treatment. Randomization, treatment, and follow-up data are depicted in a CONSORT flow diagram (**Figure 1**) .

Efficacy

At data cut-off (March 11, 2016) 71 patients (70%) reached the primary end point (PFS1) and 53 patients (52%) reached PFS2. No significant difference in PFS1 was observed between the 2 arms. Median PFS1 was 7.4 months (95% CI, 5.6-18.4) and 9.4 months (95% CI, 6.6-11.9) for the rotating and control arm, respectively (log-rank P = .37) (**Figure 2**A). One-year PFS1 was 45% (95% CI, 33%-62%) in the rotating arm and 32% (95% CI, 21%-49%) in the control arm. Additionally, no significant difference in PFS2 was observed between the rotating and control arms. The Kaplan-Meier curves separate briefly at the median resulting in relatively large differences in median PFS2 (Figure 2B). Median PFS2 was 20.2 months and 14.5 months in favor of the rotating arm (hazard ratio [HR] for stratified data, 1.02; 95% CI, 0.59-1.76; log-rank P = .86). No significant difference in time between first progression and second progression or death (PFS2II) was observed between arms. Time between first and second progression in the rotating arm was 4.0 months (95% CI, 1.8-9.2) vs 3.3 months (95% CI, 1.9-7.9) in the control arm (log-rank P = .74) (eFigure 2 in Supplement 2). Median OS for the control arm was 18.5 months (95% CI > 14.7) and 35 months (95% CI > 12.2) for the rotating arm. No significant difference in OS was observed between arms (HR stratified for MSKCC risk categories = 0.90; 95% CI, 0.51-1.58) (eFigure 3 in Supplement 2).

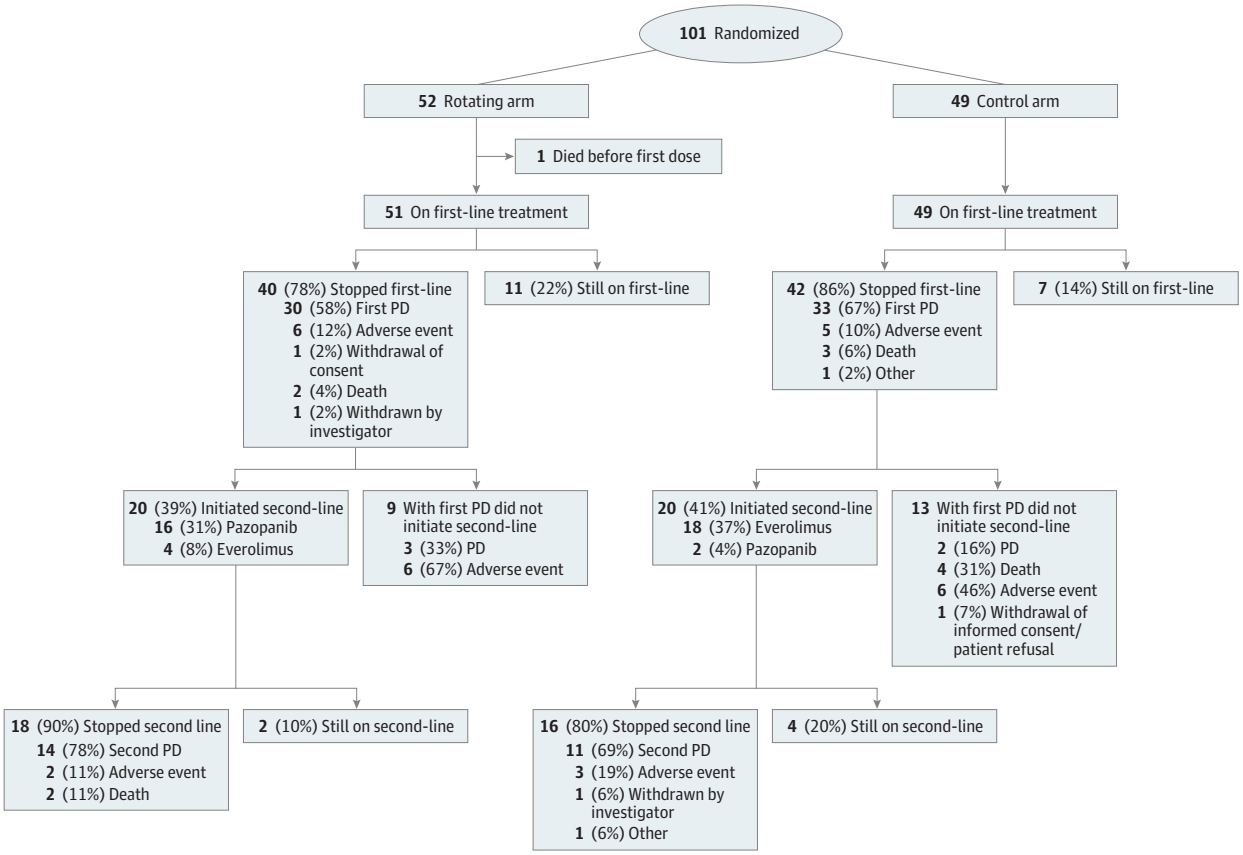
Toxic Effects

All but 1 patient took at least 1 drug dose and represent the safety population; eTable 2 in Supplement 2 lists most frequently reported adverse events marked as at least possibly related to treatment for both arms during first-line treatment. Fatigue, diarrhea, nausea and anorexia were most frequently reported as drug-related adverse events. Significantly more diarrhea possibly related to pazopanib was reported in the control arm (51% vs 27%; P = .02). Mucositis was reported in 35% of patients in the rotating arm vs 8% in the control arm (P = .001). Mucositis was related to everolimus in 68% of cases. In addition, anorexia (39% vs 22%; P = .09) and dizziness (16% vs 2%; P = .03) were more prevalent in the rotating arm. No other significant differences were detected.

Safety

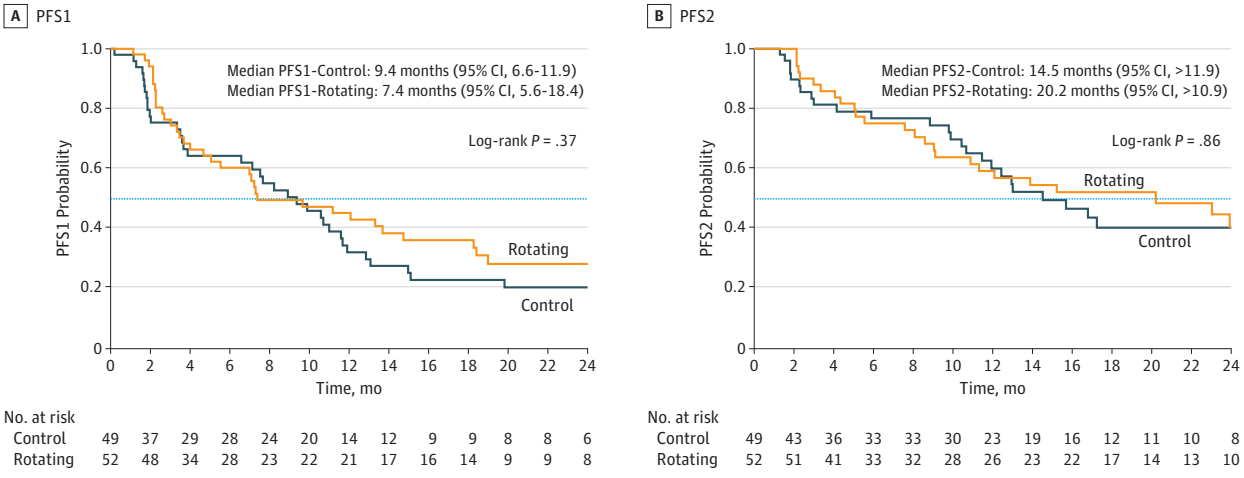
Patients in the rotating arm received a median of 2 cycles (range, 0-10) of pazopanib and 1 cycle (range, 0-9) of everolimus during first-line treatment vs 4 cycles (range 1-18) of pazopanib in the control arm. In the rotating arm, 16 patients (31%) switched to pazopanib monotherapy and 4 patients (8%) switched to everolimus monotherapy as second-line treatment (eFigure 1 in Supplement 2). In the control arm, 18 patients received everolimus as second-line treatment and 2 patients continued on pazopanib despite disease progression.

Figure 1. CONSORT Flow Diagram



A total number of participants screened for eligibility is unavailable. PD indicates progressive disease according RECIST 1.1.

Figure 2. Kaplan-Meier Analysis of PFS1 and PFS2 in the Intention-to-Treat Population



The intention-to-treat population for the control arm included 49 patients; rotating arm, 52 patients. Overall, 36 and 35 PFS1 events occurred in the control and rotating arms; 26 and 27 PFS2 events occurred, respectively. A, The stratified hazard ratio (HR) for PFS1 was 0.81 (95% CI, 0.50-1.31); unstratified HR, 0.81 (95% CI, 0.50-1.29) (stratified log-rank P = .39). B, A, The stratified HR for PFS2 was 1.02 (95% CI, 0.59-1.76); unstratified HR, 0.95 (95% CI, 0.56-1.63) (stratified log-rank P = .96). PFS1 indicates progression-free survival 1, defined as time between randomization and first PD or death; PFS2, progression-free survival 2, defined as time between randomization and second PD or death.

Thirty-seven patients (37%) required pazopanib dose reduction before first progression. There was no significant difference in the proportion of pazopanib dose reductions between treatment arms. Seven patients (14%) in the rotating arm required everolimus dose reduction before first progression (eTable 3 in Supplement 2). Main reasons for first-line drug discontinuation were progressive disease and adverse events. A total of 60 serious AEs assessed as at least possibly related to study treatment were reported in 46 patients. The incidence of possibly related serious AEs was comparable between arms (rotating: 22 patients vs control: 24 patients; $P = .69$). Study progress, AEs, and preliminary efficacy data were monitored by the Data Safety Monitoring Board throughout the study course. No adjustments in study design or conduct were recommended.

Quality of Life

Summary plots covering the FKSI-DRS symptom scale, physical functioning, and overall QoL according to QLQ-C30 are depicted in eFigures 4 through 6 in Supplement 2. No significant differences between treatment arms could be identified. In addition, no significant differences between the 2 arms in time to definitive 20% deterioration of these 3 outcome variables were observed. When looking at time to first 20% deterioration for these 3 outcome measurements, our data suggest that alternating treatment did result in early but not persistent deterioration in physical functioning (log-rank $P = .03$) (eFigure 7 in Supplement 2).

Discussion

In the ROPETAR study, the efficacy and tolerability of an 8-week regimen of alternating 2 classes of targeted drugs with proven clinical efficacy in ccRCC was prospectively evaluated. No significant difference in any of the efficacy parameters assessed between the 2 treatment strategies was observed. Also no clinical benefit was observed when considering toxic effects or QoL. Strong scientific evidence in both clinical and preclinical studies indicate the presence of reversible resistance to targeted agents in tumor cells.[10,12,14,30] This study failed to translate these findings to an active treatment regimen with 8-week rotations of different targeted agents. In our study, median PFS1 of pazopanib (9.4 months) in the control arm was within the range of previous study reports (8.4-11.1 months).[6,7] Conversely, a single-arm phase 2 trial investigating an alternating regimen of sunitinib and everolimus as first-line therapy for advanced renal cell carcinoma (EVERSUN)[31] showed a PFS of 8 months. In this trial, patients were treated with 12 weeks sunitinib 50 mg/d in a 4 weeks on and 2 weeks off schedule alternated with everolimus 10 mg/d in a 5 weeks on and 1 week off schedule. The observed PFS is comparable to the 7.4 months in the ROPETAR study. We did not observe a difference in both arms in time between first and second progression. It is important to note that the subpopulation who experienced second disease progression is likely not a representative sample of the full study population. Patients who went off-study due to toxic effects before first progression were excluded, as well as patients that died before or at the time of first progression. As a result patients in the second progression population may be less prone to toxic effects or have a more indolent or favorable natural course of disease. However, this bias is applicable to both arms.

Our hypothesis was not supported by the results of this clinical study and several questions remain. Is an interval of 2 months as chosen in the ROPETAR study optimal to reverse evolving resistance and activate an alternative resistance pathway? Most preclinical studies have focused on reversibility of proven resistance and not evolving resistance and describe regained sensitivity within up to 12 weeks.[13,18,30] Prolonged median time to progression was observed in a human Caki-1 RCC xenograft model treated with a 1-, 2-, or 3-week rotating schedule with sunitinib and everolimus.[19] A difference between the preclinical studies on drug resistance and our study is that we avoided a drug-free period for patients to avoid regrowth of tumors after withdrawal of drug.[13,30] It could be argued that pazopanib and everolimus induce similar resistance pathways thereby overriding the benefit of rotating drugs. This requires further research.

Even if PFS or OS are not prolonged, improved QoL may be of significant benefit to patients. Unexpectedly, QoL was not improved by rotating both drugs. A potential explanation is that the toxic effect profiles are overlapping and resulted in additional toxic effects. Mucositis is an example of this. Mucositis was reported more frequently in the rotating arm and may be explained by everolimus as part of its treatment regimen since 68% was assessed as at least probably related to everolimus. More pazopanib-related diarrhea was reported in the comparative arm. It could be that a rotating schedule indeed allows the gastrointestinal tract to recover from pazopanib exposure while treated with everolimus. An alternative explanation could be that a single-agent arm is compared with a dual-agent arm. All first-line toxic effects in the control arm will be automatically attributed to pazopanib while both pazopanib and everolimus may contribute in the rotating arm and a distinction has to be made by the investigator.

Conclusions

An 8-week rotating treatment strategy of pazopanib and everolimus does not provide PFS, OS, or QoL benefit to patients with metastatic or locally advanced ccRCC over continuous treatment until progression of either one of these drugs.

ARTICLE INFORMATION

Accepted for Publication: September 15, 2016.
Published Online: December 1, 2016.
doi:10.1001/jamaoncol.2016.5202

Author Affiliations: University Medical Center Utrecht, Department of Medical Oncology, Utrecht, the Netherlands (Cirkel, Groenewegen, Lolkema, Voest); Franciscus Gasthuis, Department of Medical Oncology, Rotterdam, the Netherlands (Hamberg); Erasmus MC Cancer Institute, Department of Medical Oncology, Rotterdam, the Netherlands (Sleijfer, Lolkema); Amphia Hospital, Department of Medical Oncology, Breda, the Netherlands (Loosveld); Maxima Medical Center, Department of

Medical Oncology, Eindhoven, the Netherlands (Dercksen); St Antonius Hospital, Department of Medical Oncology, Nieuwegein, the Netherlands (Los); Medical Center Leeuwarden, Department of Medical Oncology, Leeuwarden, the Netherlands (Polee); Zuyderland Medical Center, Department of Medical Oncology, Heerlen, the Netherlands (van den Berkmortel); Maastricht University Medical Center, Department of Medical Oncology, Maastricht, the Netherlands (Aarts); Elisabeth Tweesteden Hospital, Department of Medical Oncology, Tilburg, the Netherlands (Beerepoot); Isala Clinics, Department of Medical Oncology, Zwolle, the Netherlands (Tascilar); Haga Hospital, Department of Medical Oncology, Den Haag, the Netherlands (Portielje); Zuyderland Medical Center, Department of Medical Oncology, Sittard-Geleen, the Netherlands (Peters); Academic Medical Center, Department of Medical Oncology, Amsterdam, the Netherlands (Klümpen); Netherlands Cancer Institute, Department of Biometrics, Amsterdam, the Netherlands (van der Noort); Netherlands Cancer Institute, Department of Medical Oncology, Amsterdam, the Netherlands (Haanen, Voest).

Author Contributions: Dr Cirkel and Prof Voest had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Cirkel, Sleijfer, Dercksen, Groenewegen, Peters, Haanen, Voest.
Acquisition, analysis, or interpretation of data: Cirkel, Hamberg, Sleijfer, Loosveld, Los, Polee, van den Berkmortel, Aarts, Beerepoot, Lolkema, Tascilar, Portielje, Klümpen, van der Noort, Haanen, Voest.
Drafting of the manuscript: Cirkel, Hamberg, Groenewegen, Peters, van der Noort, Voest.
Critical revision of the manuscript for important intellectual content: Cirkel, Hamberg, Sleijfer, Loosveld, Dercksen, Los, Polee, van den Berkmortel, Aarts, Beerepoot, Groenewegen, Lolkema, Tascilar, Portielje, Klümpen, van der Noort, Haanen, Voest.
Statistical analysis: van der Noort.
Obtained funding: Voest.
Administrative, technical, or material support: Cirkel, Hamberg, Sleijfer, Loosveld, Polee, van den Berkmortel, Beerepoot, Lolkema, Tascilar, Peters, van der Noort, Voest.

Conflict of Interest Disclosures: Dr Cirkel reports partial reimbursement of travel expenses by Novartis. Dr Hamberg reports participation in a speakers' bureau for Astellas Pharma, Sanofi, and Janssen. Dr Sleijfer reports participation in a speakers' bureau for GlaxoSmithKline; partial reimbursement of travel expenses by Amgen; research funding by AB science and Sanofi. Dr Groenewegen reports participation in a speakers' bureau for Astellas Pharma; partial reimbursement of travel expenses by Roche Glycart. Dr Lolkema reports consulting or an advisory role for Amgen, Sanofi, and Roche Glycart; research funding by Astellas Pharma, Sanofi and Johnson & Johnson. Dr Tascilar reports partial reimbursement of travel expenses by Novartis, Astellas Pharma, Janssen and Roche Glycart. Dr Klümpen reports consulting or advisory role for Ipsen; research funding by Bayer. Dr Haanen reports consulting or an advisory role for MSD Oncology, Pfizer, and Bristol-Myers Squibb, as well as research funding by MSD and Bristol-Myers Squibb. Dr Voest reports consulting or advisory role for InteRNA, Biogeneration Ventures; research funding by Novartis, GlaxoSmithKline, Roche/Genentech, Pfizer, and AstraZeneca. No other conflicts are reported.

Funding/Support: The ROPETAR study was designed, written, and initiated by independent investigators on behalf of the Dutch WIN-O Consortium. The Dutch WIN-O Consortium received independent grants from Novartis and GlaxoSmith Kline to conduct this study. Novartis and GlaxoSmith Kline both supplied everolimus prescribed to participants in the rotating arm. Novartis and GlaxoSmith Kline had no influence on trial conduct or interpretation. A grant for clinical data management was received from the Dutch Cancer Society (grant UU 2011-5236).

Role of the Funder/Sponsor: The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The full list of Dutch WIN-O Consortium members can be found at https://www.win-o.nl/netwerkleden/ledenlijst.

Previous Presentation: The study was presented in part at the 2016 American Society of Clinical Oncology (ASCO) annual meeting; June 3-7, 2016; Chicago, Illinois.

Additional Contributions: We gratefully acknowledge all patients and their relatives for participation. We thank the members of the data safety monitoring board for their periodic data review and recommendations. We thank Roelien Kronemeijer and Nadine Korving (University Medical Center Utrecht) for their advice and trial coordination. We thank Janine Akkermans-Vogelaar (Integraal Kankercentrum Nederland, IKNL) for monitoring our clinical data. We thank the local and central data managers, Henk Botma (Netherlands Cancer Institute) in particular, and dedicated nurse practitioners for their efforts. Contributors received no compensation for their work.

REFERENCES

1. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International variations and trends in renal cell carcinoma incidence and mortality. *Eur Urol*. 2015;67(3):519-530.

2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2014.

3. Stewart SB, Thompson RH, Psutka SP, et al. Evaluation of the National Comprehensive Cancer Network and American Urological Association renal cell carcinoma surveillance guidelines. *J Clin Oncol*. 2014;32(36):4059-4065.

4. Janzen NK, Kim HL, Figlin RA, Belldegrun AS. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. *Urol Clin North Am*. 2003;30(4):843-852.

5. Escudier B, Porta C, Schmidinger M, et al; ESMO Guidelines Working Group. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014;25(suppl 3):iii49-iii56.

6. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*. 2010;28(6):1061-1068.

7. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013;369(8):722-731.

8. Motzer RJ, Escudier B, Oudard S, et al; RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 2008;372(9637):449-456.

9. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. *J Clin Oncol*. 2015;33(13):1430-1437.

10. Zama IN, Hutson TE, Elson P, et al. Sunitinib rechallenge in metastatic renal cell carcinoma patients. *Cancer*. 2010;116(23):5400-5406.

11. Porta C, Paglino C, Grünwald V. Sunitinib re-challenge in advanced renal-cell carcinoma. *Br J Cancer*. 2014;111(6):1047-1053.

12. Grünwald V, Weikert S, Seidel C, et al. Efficacy of sunitinib re-exposure after failure of an mTOR inhibitor in patients with metastatic RCC. *Onkologie*. 2011;34(6):310-314.

13. Zhang L, Bhasin M, Schor-Bardach R, et al. Resistance of renal cell carcinoma to sorafenib is mediated by potentially reversible gene expression. *PLoS One*. 2011;6(4):e19144.

14. Sharma SV, Lee DY, Li B, et al. A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations. *Cell*. 2010;141(1):69-80.

15. Das Thakur M, Salangsang F, Landman AS, et al. Modelling vemurafenib resistance in melanoma reveals a strategy to forestall drug resistance. *Nature*. 2013;494(7436):251-255.

16. Gatenby RA, Silva AS, Gillies RJ, Frieden BR. Adaptive therapy. *Cancer Res*. 2009;69(11):4894-4903.

17. Keats JJ, Chesi M, Egan JB, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood*. 2012;120(5):1067-1076.

18. Gotink KJ, Broxterman HJ, Labots M, et al. Lysosomal sequestration of sunitinib: a novel mechanism of drug resistance. *Clin Cancer Res*. 2011;17(23):7337-7346.

19. Dos Santos C, Tijeras-Raballand A, Serova M, et al. Effects of preset sequential administrations of sunitinib and everolimus on tumour differentiation in Caki-1 renal cell carcinoma. *Br J Cancer*. 2015;112(1):86-94.

20. Motzer RJ, Escudier B, Oudard S, et al; RECORD-1 Study Group. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. *Cancer*. 2010;116(18):4256-4265.

21. Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib vs first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2014;32(25):2765-2772.

22. Niraula S, Seruga B, Ocana A, et al. The price we pay for progress: a meta-analysis of harms of newly approved anticancer drugs. *J Clin Oncol*. 2012;30(24):3012-3019.

23. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours:

revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

24. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol*. 2009;27(34):5794-5799.

25. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.

26. Cella D, Yount S, Du H, et al. Development and validation of the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI). *J Support Oncol*. 2006;4(4):191-199.

27. DAMOCLES Study Group; NHS Health Technology Assessment Programme. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet*. 2005;365(9460):711-722.

28. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35(3):549-556.

29. Ko JJ, Xie W, Kroeger N, et al. The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study. *Lancet Oncol*. 2015;16(3):293-300.

30. Hammers HJ, Verheul HM, Salumbides B, et al. Reversible epithelial to mesenchymal transition and acquired resistance to sunitinib in patients with renal cell carcinoma: evidence from a xenograft study. *Mol Cancer Ther*. 2010;9(6):1525-1535.

31. Davis ID, Long A, Yip S, et al. EVERSUN: a phase 2 trial of alternating sunitinib and everolimus as first-line therapy for advanced renal cell carcinoma. *Ann Oncol*. 2015;26(6):1118-1123.