Original Investigation

Safety and Efficacy of Pazopanib Therapy Prior to Planned Nephrectomy in Metastatic Clear Cell Renal Cancer

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IMPORTANCE The role of cytoreductive nephrectomy in patients with metastatic renal cancer in the era of targeted therapy is uncertain.

OBJECTIVE To establish the safety and efficacy of upfront pazopanib therapy prior to cytoreductive nephrectomy in previously untreated patients with metastatic clear cell renal cancer.

DESIGN, SETTING, AND PARTICIPANTS Single-arm phase 2 study of 104 previously untreated patients with metastatic clear cell renal cancer recruited between June 2008 and October 2012 at cancer treatment centers with access to nephrectomy services. The minimum follow-up was 30 months.

INTERVENTIONS Patients received 12 to 14 weeks of preoperative pazopanib therapy prior to planned cytoreductive nephrectomy and continued pazopanib therapy after surgery. Treatment was stopped at disease progression.

MAIN OUTCOMES AND MEASURES The primary end point was clinical benefit (using Response Evaluation Criteria in Solid Tumors, version 1.1) prior to surgery (at 12-14 weeks). Secondary end points included surgical complications, progression-free survival (PFS), overall survival (OS), and biomarker analysis.

RESULTS Of 104 patients recruited, 100 patients were assessable for clinical benefit prior to planned nephrectomy; 80 of 104 (76.9%) were men; median [interquartile range] age, 64 [56-71] years). Overall, 84 of 100 (84% [95% CI, 75%-91%]) gained clinical benefit before planned nephrectomy. The median reduction in the size of the primary tumor was 14.4% (interquartile range, 1.4%-21.1%). No patients were unable to undergo surgery as a result of local progression of disease. Nephrectomy was performed in 63 (61%) of patients; 14 (22%) reported surgical complications. The 2 most common reasons for not undergoing surgery were progression of disease (n = 13) and patient choice (n = 9). There was 1 postoperative surgical death. The median PFS and OS for the whole cohort were 7.1 (95% CI, 6.0-9.2) and 22.7 (95% CI, 14.3-not estimable) months, respectively. Patients with MSKCC poor-risk disease or progressive disease prior to surgery had a poor outcome (median OS, 5.7 [95% CI, 2.6-10.8] and 3.9 [95% CI, 0.5-9.1] months, respectively). Surgical complications were observed in 14 (22%) of the nephrectomies. Biomarker analysis from sequential tissue samples revealed a decrease in CD8 expression (20.00 vs 13.75; $P = .05$) and significant reduction in expression of von Hippel–Lindau tumor suppressor (100 vs 40; $P < .001$) and C-MET (300 vs 100; $P < .001$) and increased programmed cell death ligand 1 expression (0 vs 1.5; $P < .001$) in the immune component. No on-treatment biomarker correlated with response.

CONCLUSIONS AND RELEVANCE Nephrectomy after upfront pazopanib therapy could be performed safely and was associated with good outcomes in patients with intermediate-risk metastatic clear cell renal cancer.

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Editorial

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The role of cytoreductive nephrectomy for patients with advanced clear cell renal cancer (ccRCC) who present with a synchronous renal mass and metastasis is uncertain. The current standard of care is cytoreductive nephrectomy followed by vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) therapy.[1] The use of nephrectomy in metastatic disease was established prior to the development of VEGF TKIs.[2,3] This sequence has not been prospectively evaluated in the era of VEGF-targeted therapy, although large recent retrospective series suggest that nephrectomy is still associated with a survival benefit in unselected patients.[4] A potential problem with this sequence is that there is a substantial delay in starting VEGF-targeted therapy while patients are recovering from the nephrectomy. This is of particular concern for patients with aggressive disease or poor prognostic features for whom any delay in disease control may be detrimental.[4-6]

An alternative approach is to give upfront systemic therapy prior to the nephrectomy. This has theoretical advantages in that systemic therapy can commence more rapidly, and there may be substantial shrinkage of the primary tumor, facilitating surgery. It is also possible that this upfront approach selects out patients with rapidly progressive VEGF-resistant disease who have a short life expectancy and may not benefit from nephrectomy.[5,7] There are also potential risks to this approach. Nephrectomy may enhance the systemic response to VEGF therapy by reducing the tumor burden. Also, substantial time off systemic therapy is required during the perioperative period, which may allow for the development of resistance to therapy. Finally, it has been reported in previous small safety studies that although this upfront approach is feasible, surgery may be more complex due to additional treatment-related necrosis and delayed wound healing.[7,8] Therefore, in this study we planned to prospectively evaluate the efficacy of this upfront approach by giving up to 14 weeks of pazopanib hydrochloride therapy prior to nephrectomy.

Biomarker analysis from tissue sampled prior to therapy has not resulted in predictive markers in ccRCC.[9] We hypothesized that tissue taken before and during therapy may facilitate biomarker discovery. Due to the nature of the design of this study, sequential tissue was available from pretreatment samples and at the time of surgery, allowing for assessment of biomarker evaluation on treatment.

Key Points

Question Is pazopanib therapy prior to cytoreductive nephrectomy safe and efficacious in patients with previously untreated metastatic renal cancer?

Findings In this phase 2 study of 104 patients, most gained clinical benefit with pazopanib therapy. A majority were able to undergo nephrectomy, and biomarker analysis revealed substantial changes to key proteins (vascular endothelial growth factor receptor 2 and programmed cell death ligand 1).

Meaning Nephrectomy after upfront pazopanib therapy is feasible and associated with good outcomes in selected patients.

Methods

Patient Population

The study population included treatment-naive patients with histologically confirmed metastatic ccRCC. Patients were required to be fit for both pazopanib therapy and nephrectomy, have adequate end organ function, be able to give informed consent, and have an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients who had previously undergone nephrectomy for renal cancer were excluded. Other exclusion criteria focused on contraindications for pazopanib therapy such as uncontrolled bleeding, hypertension, or cardiovascular disease.

This was a multicenter single-arm trial enrolling from 12 centers across the United Kingdom. The study received appropriate ethical and regulatory approval from the London-South East Research Ethics Committee (NCT01512186). All patients provided written informed consent.

Study Design and Sample Size

Patients were planned to receive 12 to 14 weeks of pazopanib hydrochloride (800 mg daily) prior to cytoreductive nephrectomy (open or laparoscopic), which took place at least 48 hours after the last dose of systemic treatment. A 14-day treatment break was required after surgery. Pazopanib therapy was then continued every 6 weeks, until disease progression was recorded. Patients who exhibited disease progression during the treatment break were allowed to continue pazopanib therapy if it was deemed to be of clinical benefit. Dose reductions of pazopanib followed standard guidelines. Surgery could be brought forward on the basis of clinical grounds after discussion with the medical monitor. Treatment delays of up to 28 days were permitted.

The primary end point of the trial was to achieve a clinical benefit rate of greater than 75% at the time of the presurgical tumor assessment. Clinical benefit was defined as no clinical or radiological progression of disease (Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]). The numbers of fully evaluable patients (95) were generated using Simon 2-stage optimal design. The study had a 90% chance of concluding that pazopanib is active if the true clinical benefit rate was 75% or more but only a 5% chance of concluding it was active if the clinical benefit was less than 60%. An interim analysis occurred after recruitment of the first 34 patients, 22 of whom needed stabilization to proceed to the second stage. Because the primary end point was clinical benefit at 12 to 14 weeks, it was planned to recruit approximately 125 patients to account for patients who drop out during this period.

Secondary end points included progression-free survival (PFS) by RECIST v1.1, overall survival (OS), the frequency of adverse events by Common Terminology Criteria for Adverse Events, version 4.0, and the evaluation of surgical complications by Clavien-Dindo classification. Disease assessment was performed at baseline, 6 weeks into systemic treatment, before nephrectomy (12-14 weeks after initiation of pazopanib

therapy), 6 weeks after nephrectomy, and then at intervals of 12 weeks. Radiology review occurred according to investigator assessment.

Statistical Analysis

The primary end point was calculated as clinical benefit rate, with 95% confidence interval. Progression-free and overall survival were assessed using the Kaplan-Meier method. July 31, 2014, was used as a censoring date for patients who had not experienced disease progression or died. In survival analysis, the prognostic value of the baseline factors was assessed via Cox proportional hazards regression model. The assumption of proportional hazards was tested by examining plots of complementary log-log(event time) vs log(time). Intercooled STATA, version 13.0 (STATA Corp), was used for the statistical analysis.

Biomarker Analysis

A tissue microarray was constructed from biopsy and nephrectomy tissue samples. The following antibodies were used to assess biomarker expression: PDL-1 (Abcam), C-MET (Life Technologies), hypoxia-inducible factor 1α (HIF-1α) (Novus Biologicals), VEGFR2 (Cell Signaling), and von Hippel-Lindau tumor suppressor (VHL) (BD Pharmingen). Expression in untreated and treated samples was compared using validated immunohistochemistry protocols for each antibody. A single pathologist (G.T.) scored the immunohistochemical expression. The immunohistochemical scoring was performed independently and blinded to patient outcome data for each antibody.

Multiple samples were taken in the nephrectomy samples (n = 5) where possible to allow for intratumoral heterogeneity (median scores were taken). A 2-sample *t* test was used to test the difference of biomarker values between treated and untreated patients. The prognostic significance of biomarkers was assessed via Cox proportional hazards regression model.

Results

Patient Characteristics at Diagnosis and at Surgery

One hundred four patients were recruited and received the study drug. Patients' baseline demographic characteristics are presented in the **Table**. Eighty of 104 patients (76.9%) were men. The median age was 64 years (interquartile range [IQR], 56-71 years). Liver or bone metastases were present in 44 patients (42%), while 63 patients (61%) had T3-T4 tumors. The median size of the primary tumor was 10 (IQR, 8.3-11.6) cm. Three Memorial Sloan Kettering Cancer Center (MSKCC) risk scores could not be collected; therefore, of the remaining 101 patients, 83 (82%) had intermediate-risk disease, and 18 (18%) had poor-risk disease.

Efficacy of Upfront Pazopanib Therapy

Of the 104 patients recruited, 100 patients were assessable for clinical benefit prior to planned nephrectomy (Consolidated Standards of Reporting Trials diagram in **Figure 1**). Four patients were not assessable because they discontinued pazopanib therapy as a result of adverse effects prior to radiological assessment for clinical benefit. The primary objective

Table. Patient Demographic and Clinical Characteristics[a]

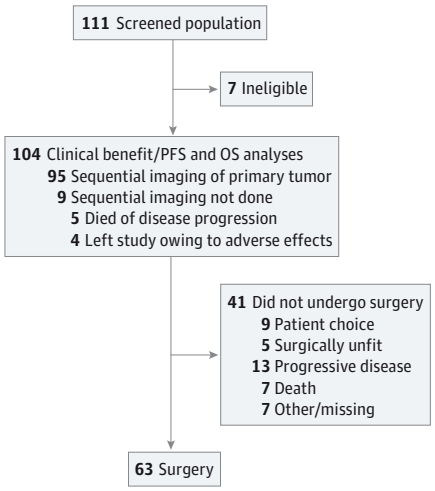
Baseline Characteristics	Total Population (N = 104)	Poor-Prognosis Population (n = 18)
Age, median (IQR), y	63.8 (56.3-70.8)	64.1 (59.7-69.9)
Sex		
Female	24 (23.1)	5 (29.5)
Male	80 (76.9)	12 (70.5)
MSKCC prognostic risk[b]		
Intermediate	83 (82.0)	NA
Poor	18 (18.0)	18 (100)
Performance status		
0	29 (28.7)	1 (5.9)
1	63 (62.4)	9 (52.9)
2	9 (8.9)	7 (41.2)
Sites of metastases		
Lung	90 (86.5)	16 (88.9)
Bone	29 (27.9)	8 (44.4)
Lymph node	48 (46.1)	12 (66.7)
Liver	15 (14.4)	4 (22.2)
Radiologic T stage at diagnosis		
T1	10 (9.8)	1 (5.6)
T2	29 (28.4)	5 (27.8)
T3	52 (51.0)	8 (44.4)
T4	11 (10.8)	4 (22.2)
Primary tumor size, median (IQR), cm	10.0 (8.3-11.6)	11.3 (9.9-12.2)

Abbreviations: IQR, interquartile range; MSKCC, Memorial Sloan Kettering Cancer Center; NA, not applicable.

[a] Unless otherwise noted, data are reported as number (percentage) of participants.

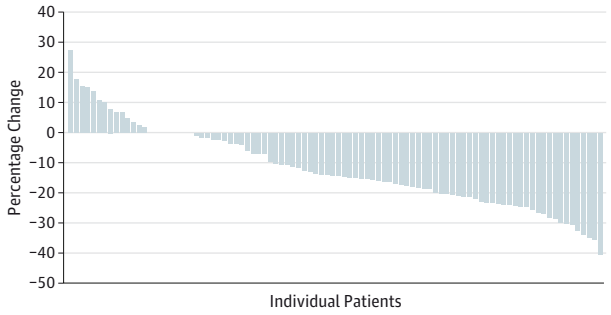
[b] MSKCC risk scores collected for 101 of the 104 participants.

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram



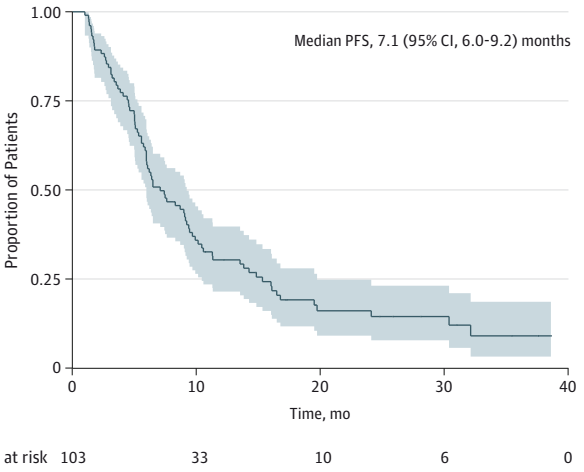
OS indicates overall survival; PFS, progression-free survival.

Figure 2. Percentage Change of Primary Renal Carcinoma Following Therapy With Pazopanib



Median size reduction of the primary tumor was 14.4% (interquartile range, 1.4%-21.1%) (n = 95).

Figure 3. Kaplan-Meier Curve Showing Progression-Free Survival for the 104 Patients in the Intention-to-Treat Population



The shaded area around the median represents 95% confidence intervals.

of the trial was achieved, with 84 of 100 (84% [95% CI, 75%-91%]) patients achieving clinical benefit. Thirteen (13%) patients had a partial response to therapy, and 16 (16%) had progression of disease; the remaining 71 patients (71%) had stable disease.

The median (range) duration of therapy prior to surgery was 13 (11-14) weeks. The median size of the primary tumor before and after pazopanib therapy was 10.0 (IQR, 8.3-11.6) and 8.3 (IQR, 6.8-10.9) cm, respectively. Median size reduction of the primary tumor was 14.4% (IQR, 1.4%-21.1%) (**Figure 2**). The median PFS and OS for the 104 patients enrolled was 7.1 (95% CI, 6.0-9.2) and 22.7 (95% CI, 14.3 to not estimable) months, respectively (**Figure 3**). Patients who did not achieve clinical benefit had shorter overall survival compared with those who achieved clinical benefit (median overall survival, 3.9 [95% CI, 0.5-9.1] vs 24.0 [95% CI, 18.4 to not estimable] months), hazard ratio, 3.92 [95% CI, 1.78-8.63]) (eFigure 1 in the Supplement). Eighteen (18%) patients had MSKCC poor-risk disease, of whom 7 (39%) had disease progression as the presurgery response; and only 8 of 18 (44%) underwent surgery. These MSKCC poor-risk patients had a median PFS and OS of 3.9 (95% CI, 1.7-7.5) and 5.7 (95% CI, 2.6-10.8) months, respectively (eFigure 2 in the Supplement). Progression of disease during the 6-week treatment interval occurred in 25% of the patients who underwent nephrectomy. Univariable survival analysis for age; sex; MSKCC score; tumor T stage; presence of bone, brain, or liver metastasis; and performance status at baseline identified only MSKCC score as a significant prognostic marker for PFS (hazard ratio, 2.46 [95% CI, 1.44-4.21]).

Evaluation of Surgical Safety

Of the 104 patients, 65 (63%) underwent nephrectomy. The 3 most common reasons for not undergoing nephrectomy were progression of systemic disease (n = 13), patient choice (n = 9), and the patient being surgically unfit (n = 5).

Forty-three (68%) patients underwent open nephrectomy, with the remainder undergoing laparoscopic nephrectomy. The median postoperative hospital stay was 7 (IQR, 5-8) days. Median surgical time was 3 (IQR, 1.8-3.9) hours. There was 1 surgery-related death. Surgical complications were observed in 14 (22%) of the nephrectomies, including bleeding (5 [8%]), delayed wound healing (4 [6%]), splenectomy (2 [3%]), and elevated creatinine level (1 [2%]) (eTable 1 in the Supplement). Of the surgical complications, 2 (3%) were grade 3 or 4 (Clavien-Dindo). The median (IQR) blood loss was 450 (100-725) mL; surgical time, 3 (1.8-3.9) hours; and hospital stay, 7 (5-8) days (eTable 1 in the Supplement). Fifty-four (90%) of the operations revealed a T2 to T4 tumor, underlining the advanced stage of disease of these patients.

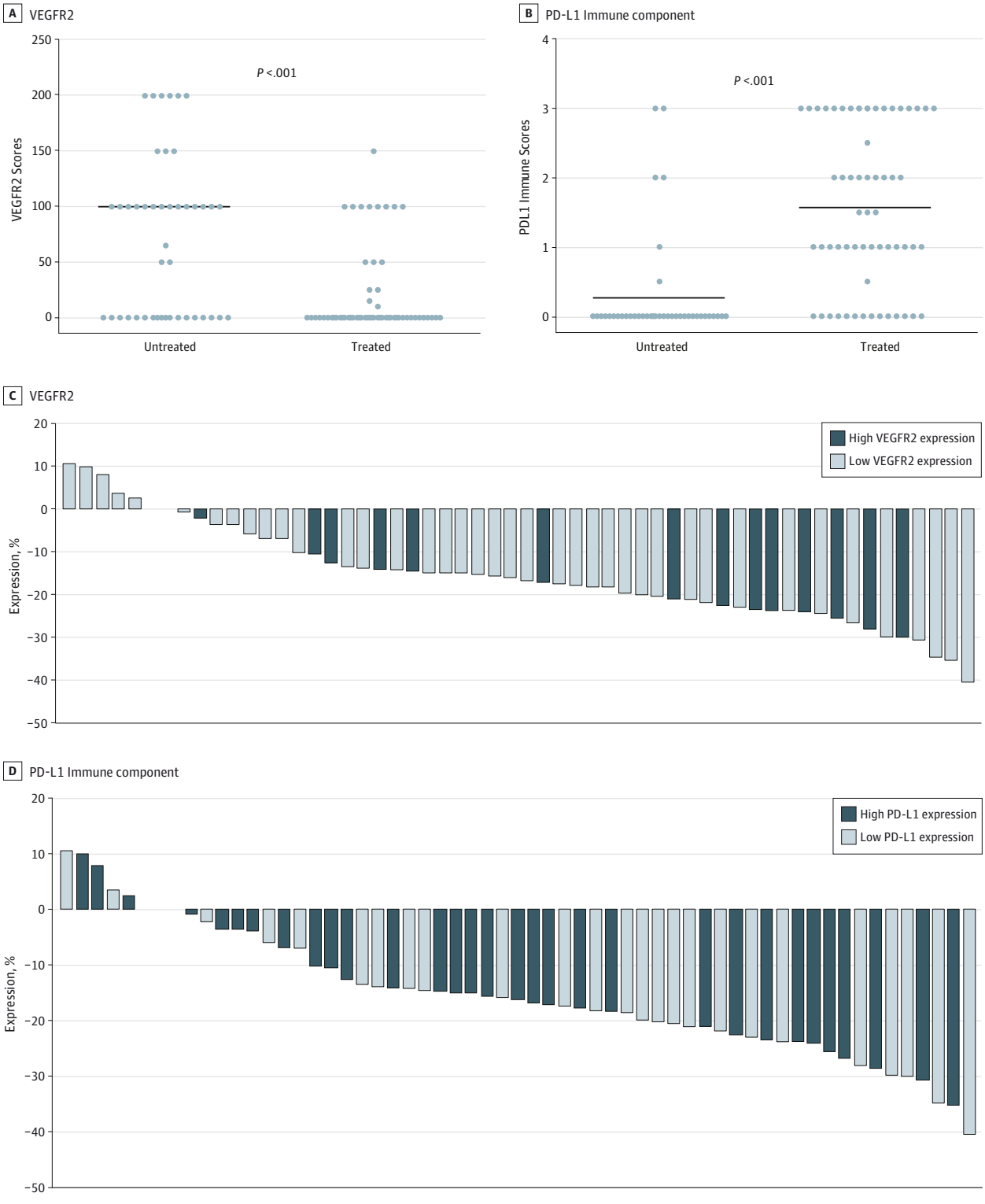
Toxicity Profile

Adverse events were in line with those previously reported with pazopanib therapy.[10] Grade 3 or 4 adverse events occurred in 28% of patients. The most common toxic effects (any grade) were fatigue (88 [85%]), diarrhea (55 [53%]), hypertension (52 [50%]), and hand and foot syndrome (33 [32%]) (eTable 2 in the Supplement). Pazopanib dose was reduced in 26 patients (25%) before surgery. Four patients discontinued therapy as a result of adverse effects.

Biomarker Analysis

There was a significant decrease of expression of VEGFR2 (100 vs 0; $P < .001$), C-MET (300 vs 100; $P < .001$), and VHL (100 vs 40; $P < .001$) after pazopanib therapy (**Figure 4** and eFigure 3 in the Supplement). Expression of programmed cell death ligand 1 (PD-L1) in the immune component increased with therapy (0 vs 1.5; $P < .001$), while CD8 expression decreased (20.00 vs 13.75; $P = .05$). Further biomarker analysis of patients receiving treatment showed that none of the biomarkers were correlated with survival outcome or response (Figure 4C and D and eFigure 4 and eTable 3 in the Supplement). Intratumoral biomarker variability was evident for PD-L1 expression on multiple testing, with only 1 (8%) of 14 patients consistently scoring the same when 5 samples from the same tumor were analyzed.

Figure 4. Molecular Markers Before and After Pazopanib Therapy



A, Significant decrease of expression of vascular endothelial growth factor receptor 2 (VEGFR2) ($P < .001$). B, Significant increase of programmed cell death ligand 1 (PD-L1) in the immune component ($P < .001$). Each dot represents a point value; the horizontal line indicates the median. Change also occurred with C-MET (n = 59) ($P < .001$), CD8 (n = 62) ($P = .05$), and von Hippel–Lindau tumor suppressor (n = 57) ($P < .001$) after pazopanib therapy (eFigure 3 in the Supplement). C and D, Waterfall plot comparing VEGFR2 and PD-L1 immune component expression on therapy and response; each bar represents a study participant. None of these biomarkers correlated with response in the primary tumor.

Discussion

There is a lack of prospective data for patients with ccRCC who present with a synchronous renal tumor and metastatic disease in the era of targeted therapy. These patients have a poor outcome, which is supported by retrospective series and prognostic scoring systems.[4,5] There is also uncertainty about the role and timing of nephrectomy. In this study, 12 to 14 weeks of pazopanib therapy was given prior to nephrectomy. The aim was to induce stability of disease prior to nephrectomy in more than 75% of patients, avoiding potential progression and clinical deterioration during the preoperative surgical period. The PFS and OS results (median of 7.1 and 22.7 months, respectively) were in line with those seen for similar risk groups in the pivotal randomized VEGF-targeted therapy trials in which the majority of patients previously underwent nephrectomy.[10-12] Survival analysis showed that the prognostic factors in this specific group of patients are similar to those in unselected patients. The MSKCC prognostic score was significant.

This approached seemed to be safe, with low surgical morbidity, acceptable levels of surgical complications, and low surgical-related mortality (2%). However, there were areas of concern. Delays in wound healing, thought to be related to VEGF-targeted therapy, were reported in this and other smaller series.[7] Also, 39% of patients did not undergo nephrectomy. This is higher than figures for nephrectomy prior to systemic therapy and is probably a result of patients with primary progressive disease not undergoing nephrectomy.[2] It seems sensible not to perform nephrectomy on these patients with primary progressive metastatic disease because it spares them a procedure that causes morbidity but may not significantly improve outcome. It also allows them to switch to potentially more effective systemic therapies.[13,14] Patients with progression of disease at 14 weeks (the time of assessment) had a poor outcome, which justifies this approach (eFigure 1 in the Supplement). A second smaller group did not undergo nephrectomy because of the development of morbidity. Pazopanib therapy is associated with a spectrum of adverse effects, which may have contributed to this.[10] This group of patients is a concern because nephrectomy prior to pazopanib therapy may have been possible and may have improved outcome. Finally, a group chose not to have nephrectomy. Some of these were patients who were responding well to therapy and were reluctant to stop therapy for surgery. This group of patients is small but had a good outcome (data not shown). In an era in which there is uncertainty regarding the benefits of cytoreductive nephrectomy, this appears to be a pragmatic approach and not necessarily of concern.

Another group of patients, requiring particular attention, are those with MSKCC poor-risk disease at baseline. These patients had a poor outcome irrespective of whether they underwent surgery (median overall survival, 5.7 [95% CI, 2.6-10.8] months) (eFigure 2 in the Supplement). Previous retrospective analysis of other smaller prospective series with sunitinib malate suggested that nephrectomy was not recommended in these patients.[4,15] Our data support this recommendation. These issues will be further addressed within 2 randomized trials testing the role and timing of nephrectomy in metastatic ccRCC (NCT00930033, NCT01099423). Comparisons with pazopanib and sunitinib are not possible in this setting, largely because of the small size of the studies and variability in protocol design.[7] Both drugs have clinical benefit rates of greater than 70% in this setting, although the sunitinib trials focused mainly on safety rather than efficacy. Previous noninferiority studies show that these agents are noninferior in terms of efficacy, with differing adverse event profiles.[11] Our results support these findings. The data presented here are, to our knowledge, the most robust thus far, and pazopanib appears well tolerated and efficacious.

To date, pretreatment predictive biomarkers have not been identified for VEGF-targeted therapy.[9] We hypothesized that biomarker analysis after a period of therapy could identify subgroups of patients who benefit from VEGF-targeted therapy. It was possible to test this hypothesis in our trial due to the nature of the design and the relatively large numbers compared with previous studies.[16] Results showed significant decreases in VEGF-related biomarkers (HIF, VEGFR2, and VHL) with therapy. However, suppression of VEGF-related biomarkers did not correlate with outcome. It may be that the timing of the analysis was too early because the majority of patients were still benefiting from therapy. A third sample at progression would have potentially helped address this issue. We explored the effect of pazopanib on PD-L1 and MET expression, both of which are active targets in ccRCC after VEGF-targeted therapy.[13,14] Results showed significant decreases to VEGF-related proteins such as VEGFR2, as expected.[16] However, pazopanib therapy was also associated with increased PD-L1 expression in the immune component in conjunction with a decrease in CD8 count. Both PD-L1 and CD8 expression are of prognostic significance in renal cancer.[17] These results underline the potential immunogenic effects of VEGF TKIs and the problems associated with archived untreated tissue for PD-L1 biomarker analysis in VEGF-resistant ccRCC.[14]

Intratumor heterogeneity of PD-L1 expression seen in our treated samples further complicates these issues. Cabozantinib s-malate is a MET (and VEGF) inhibitor with activity in VEGF-resistant metastatic ccRCC.[13] Pazopanib therapy reduced MET expression, again calling into question the value of historical tissue samples for biomarker expression. Although significant changes occurred to a spectrum of proteins, none correlated with response, suggesting that on-treatment biomarker expression may not be a breakthrough in biomarker discovery in this setting as originally hoped.

This work has shortcomings, notably the fact that the trial was not randomized and the duration of therapy prior to the nephrectomy was fixed. In addition, the biomarker analysis was limited because many of the patients with progressive disease did not undergo surgery and there were challenges around processing nephrectomy biopsy tissue. Finally, some of the details regarding the surgery, such as thrombectomy and use of anticoagulation therapy, were not collected. Nevertheless, this clinical approach is potentially attractive to subsets of patients, particularly those who are keen to start therapy quickly and those who do not have MSKCC poor-risk disease.

Conclusions

Upfront targeted therapy does not adequately reduce the size of the primary tumor to recommend pazopanib therapy prior to cytoreductive nephrectomy to facilitate surgery. However, the approach achieved rapid control of disease in the majority of patients and was associated with acceptable outcomes. Pazopanib seems to be an attractive agent in this setting because of its acceptable adverse event profile.[11] Our results question the role of cytoreductive nephrectomy in patients with MSKCC poor-risk disease in a single-arm prospective study for the first time.

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Author Contributions: Dr Powles had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Powles, Sarker, Chowdhury, Crabb.
Acquisition, analysis, or interpretation of data: Powles, Sarwar, Stockdale, Sarker, Boleti, Protheroe, Jones, Chowdhury, Peters, Oades, O'Brien, Sullivan, Aitchison, Beltran, Worth, Smith, Michel, Trevisan, Harvey-Jones, Wimalasingham, Sahdev, Ackerman, Crabb.
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