VOLUME 27 · NUMBER 2 · JANUARY 10 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Metastatic Sarcomatoid Renal Cell Carcinoma Treated With Vascular Endothelial Growth Factor–Targeted Therapy

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Submitted May 6, 2008; accepted August 21, 2008; published online ahead of print at www.jco.org on December 8, 2008.

Presented in part at the 6th International Kidney Cancer Association Symposium, Chicago, IL, October 11-13, 2007, and at the 2008 Genitourinary Cancer Symposium, San Francisco, CA, February 14-16, 2008.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/09/2702-235/$20.00

DOI: 10.1200/JCO.2008.18.0000

ABSTRACT

Purpose
Metastatic renal cell carcinoma (mRCC) with sarcomatoid differentiation is an aggressive disease that is associated with poor outcomes to chemotherapy or immunotherapy. The utility of vascular endothelial growth factor (VEGF)–targeted therapy in patients with this disease is unknown.

Patients and Methods
Patients who had mRCC with sarcomatoid features in the primary tumor and who were treated with VEGF-targeted therapy were retrospectively identified. Pathology slides were reviewed to determine the percentage of sarcomatoid differentiation. Objective response rate, percentage of tumor burden shrinkage, progression-free survival (PFS), and overall survival (OS) were determined.

Results
Forty-three patients who had sarcomatoid mRCC were identified. The median percentage of sarcomatoid features was 14% (range, 3% to 90%). Patients were treated with either sunitinib (49%), sorafenib (28%), bevacizumab (19%), or sunitinib plus bevacizumab (5%). Partial responses were observed in eight patients (19%); 21 patients (49%) had stable disease; and 14 patients (33%) had progressive disease as their best response. Partial responses were limited to patients who had underlying clear-cell histology and less than 20% sarcomatoid elements. Median tumor shrinkage was −2% (range, −85% to 127%), and 53% achieved some degree of tumor shrinkage on therapy. Median PFS and OS were estimated to be 5.3 months and 11.8 months, respectively.

Conclusion
Patients who have mRCC and sarcomatoid differentiation can demonstrate objective responses and tumor shrinkage to VEGF-targeted therapy. Patients who have clear-cell histology and a lower percentage of sarcomatoid differentiation may have better outcomes with VEGF-targeted therapy.

J Clin Oncol 27:235-241. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Sarcomatoid differentiation in renal cell carcinoma (RCC) is a growth pattern characterized by malignant spindle-shaped cell histology.[1] It is not a distinct histologic entity; rather, it can be observed across all RCC subtypes, including clear-cell, papillary, chromophobe, unclassified, and collecting-duct carcinomas.[2] Most patients are symptomatic at diagnosis, and abdominal pain and hematuria are commonly observed. Sarcomatoid tumors are characterized by a relatively high incidence of metastases to the lung and bone at presentation.[3] Patients who have metastatic sarcomatoid RCC have a poor prognosis and have a median overall survival (OS) of 3 to 10 months from the time of diagnosis.[4-8] Patients who have localized disease have 2-year and 5-year survival rates of only 25% to 40% and 19%, respectively.[3,9]

Sarcomatoid differentiation is thought to represent transformation of the RCC malignancy to a higher grade, therefore Fuhrman grade 4 by definition (Fig 1.). With regard to immunohistochemical markers, these tumors are generally positive for AE1/AE3, epithelial membrane antigen, and vimentin, which supports an epithelial origin.[10] Staining for actin, desmin, and *S*-100 are usually negative. Vascular endothelial growth factor (VEGF), Kit, and S6 kinase have been expressed in the majority of sarcomatoid specimens.[4,6,10-13] Fascin expression has been reported in 62% of patient cases, and it may be an independent predictor of metastatic disease.[12] Hypoxia inducible factor-1α, carbonic anhydrase IX, and glucose transporter 1 were overexpressed the majority of clear-cell sarcomatoid, but not in non–clear-cell sarcomatoid, RCC specimens in one series.[4] The genetic alterations in sarcomatoid RCC are not well understood. Mutations of p53 may be associated with sarcomatoid differentiation.[14]

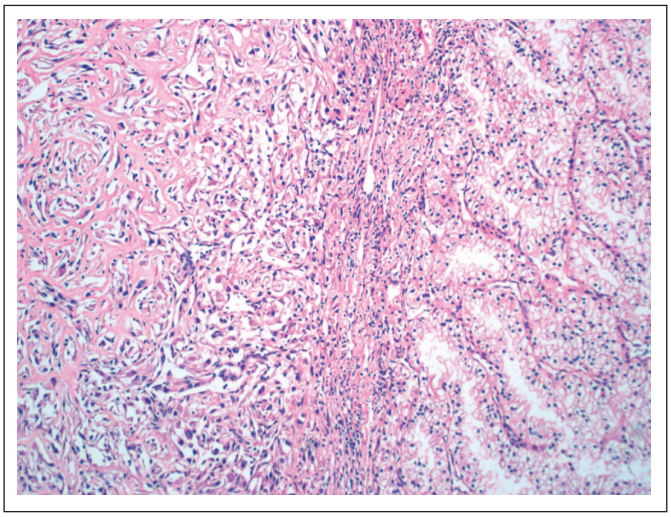

Fig 1. Sarcomatoid differentiation in clear-cell renal cell carcinoma. The right side of the image represents conventional clear-cell renal cell carcinoma, with large nests of clear cells separated by delicate vascular network. The left side represents the sarcomatoid differentiation, with spindle-shaped pleomorphic cells embedded in a dense, osteoid-like stroma.

The prognostic implication of the proportion of sarcomatoid component within an RCC tumor is an area of controversy. A higher proportion of sarcomatoid differentiation has been associated with worse survival in some series.[4,9] Others have reported that the proportion of sarcomatoid elements is a poor prognostic indicator only in stages I and II.[7] However, other investigators have reported that the percentage of sarcomatoid elements is not associated with clinical outcomes.[6,8,15,16] This matter is additionally complicated, because no standard method to determine the percentage of sarcomatoid elements within the RCC tumor has been defined.

Patients who have RCC and sarcomatoid features have historically demonstrated limited responses to treatment (Table 1). There are several case reports that describe long-term responses to doxorubicin-based chemotherapy.[23-27] Retrospective reviews have been less encouraging, and the few prospective trials performed have involved relatively small numbers of patients and had disappointing results.[20,21] Several studies have shown that these tumors can respond to chemotherapy and/or immunotherapy.[5,6,8,19,28] However, the available data is difficult to interpret, as the precision of the published information is not optimal, and the results may have been influenced by case-selection bias.

Currently, therapy directed against VEGF is a standard of care in metastatic RCC.[29-31] The major trials that defined the benefit of this therapy did not report the percentage of patients who had sarcomatoid elements; thus, there are no data on how patients who have sarcomatoid metastatic RCC respond to VEGF-targeted therapy. On the basis of the above considerations, patients who had sarcomatoid metastatic RCC and who received VEGF-targeted therapy were retrospectively identified, and clinical outcome was recorded. The clinical and pathologic factors associated with outcome also were investigated.

PATIENTS AND METHODS

Patients

Patients with metastatic RCC with sarcomatoid features who were treated with VEGF-targeted therapy (ie, sunitinib, sorafenib or bevacizumab) at the Cleveland Clinic Taussig Cancer Institute were retrospectively identified. The patients were selected on the basis of the criteria of a sarcomatoid tumor (per the existing pathology report) and the receipt of VEGF-targeted therapy during the time period of March 2004 to September 2007. The majority of patients (n = 25) were treated outside of a clinical trial, and their outcomes are reported first in this study. Eighteen patients were treated on previously reported trials; sunitinib for cytokine-refractory mRCC in a compassionate-use study (n = 6);[32] the advanced RCC sorafenib expanded access trial (n = 4);[33] a phase II sunitinib study (n = 3);[34] a phase I trial of sunitinib and bevacizumab (n = 2);[35] a phase III randomized trial that compared sunitinib to interferon alfa (n = 2);[30] and the phase III sorafenib trial (n = 1).[36]

Pretreatment patient and disease characteristics were collected. All clinical information was collected through chart review on an existing institutional review board–approved protocol (IRB 4970). Physical examinations and laboratory tests were performed at baseline and were repeated every 4 to 6 weeks. Tumor assessments by radiologic methods (ie, computed tomography scans) were done at baseline and were repeated every two cycles (approximately every 8 to 12 weeks). Tumor response was measured by investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) criteria,[37] and objective responses were confirmed on two consecutive measurements at least 4 weeks apart. Objective response per RECIST criteria, percentage of total tumor burden change, time to progression, and overall survival were recorded. Tumor shrinkage, defined as the percentage of total tumor burden change (regression or growth), also was measured.

Pathology Review

Sarcomatoid tumors were initially identified by review of existing pathology reports from nephrectomy specimens. Subsequently, all available nephrectomy pathology slides were retrieved and rereviewed by a single expert genitourinary pathologist (M.Z.), who was blinded to patient outcome. The classification of RCC subtypes and the presence of sarcomatoid differentiation were confirmed on the basis of the 2004 WHO classification of renal tumors.[38] The percentage of sarcomatoid elements in each tumor was estimated in a consistent fashion as follows: Every slide from each case was examined individually. The area of the sarcomatoid component relative to the tumor was estimated on each slide. The mean percentage of sarcomatoid component relative to the tumor from each slide was added to obtain the total estimated sarcomatoid percentage for each patient.

To compare outcomes in patients who had sarcomatoid components with those who did not have sarcomatoid components, patients who had sarcomatoid components were matched to patients in a metastatic RCC database who had no sarcomatoid elements present. Patients who had non–clear-cell histology were excluded from this analysis, because the database used for the matching is comprised primarily of patients who had metastatic RCC with clear-cell histology only. Patients were matched on type of anti-VEGF therapy received, sex, prognostic risk group,[39] and age (±10 years in all but eight patient cases).

Statistical Analysis

Descriptive statistics, such as frequency counts, medians, and ranges, were used to characterize the patient sample. Progression-free survival (PFS) was measured from the start of anti-VEGF therapy to the development of objective disease progression, intolerable adverse effects, or death—whichever came first. OS was measured from the start of therapy to death or last follow-up. Both outcomes were summarized by using the Kaplan-Meier method. A recursive partitioning algorithm, which identified 20% as a cut point, was used to group patients on the basis of the percentage of the tumor comprised of sarcomatoid elements.

Fisher's exact test was used to compare objective response between patient groups; the Wilcoxon rank sum test was used for comparisons of tumor shrinkage; and the log-rank test was used for comparisons of PFS and OS. The data derived from the matched-pairs analysis were analyzed by using McNemar's test for objective response, the Wilcoxon signed rank test for tumor shrinkage, and the sign test for PFS. All data analyses were performed by using SAS version 9.1 (SAS Institute, Cary, NC) and StatXact 7 (Cytel Software Corp, Cambridge MA).

Table 1. Select Reported Treatment Regimens in Sarcomatoid RCC

Treatment by Study	No. of Patients	Objective Response		Median Overall Survival (months)
		No. and Type	Duration (months)	
Sella et al 1987*[3]				
CYVADIC	7	2 CR	50	7
			65	
Culine et al 1995*[17]				
CYVADIC	3	1 PR	12	—
DECAV	3	2 PR	6	
			8	
DI	2	1 PR	5	
IFN-α	4	0 PR		
Wu et al 1998*[18]				
High-dose IL-2	2	0 PR		13.8
Moderate-dose IL-2	2	0 PR		
IFN-α–based therapy	2	0 PR		
Wood et al 1999†[19]				
DI + IFN-α	12	1 CR	$\geq$ 6	—
		1 PR	$\geq$ 5	
Cangiano et al 1999*[8]				
High-dose IL-2	9	2 PR		80% at 20 months
Low-dose IL-2	5	0 PR		3
TIL/IFN-α + IL-2	9	1 CR		
		2 PR		8
Escudier et al 2002†[20]				
DI	23	0 PR		
		6 SD		3.9
Mian et al 2002*[6]				
IFN-α–based, IL-2–based, or IFN-γ–based therapy‡	86	28 PR		8.5
		16 SD		
Nanus et al 2004†[21]				
Doxorubicin + gemcitabine	10	2 CR	$\geq$ 4	—
			$\geq$ 21	
		1 PR	4	
		2 SD	4	
			11	
Kwak et al 2007*[5]				
IFN-α or FU + IL-2 + IFN-α	32		NA§	10.0
Amato et al 2007†[22]				
Gemcitabine + capecitabine + thalidomide + IFN-α	4	2 PR	4	
			7	—

Abbreviations: RCC, renal cell carcinoma; CYVADIC, cyclophosphamide + vincristine + doxorubicin + dacarbazine; CR, complete response; PR, partial response; DECAV, dacarbazine + cyclophosphamide + cisplatin + doxorubicin; DI, doxorubicin + ifosfamide; IFN-α, interferon alfa; IL-2, interleukin-2; TIL, tumor-infiltrating lymphocyte; SD, stable disease; IFN-γ, interferon gamma; FU, fluorouracil; NA, not available.
*Retrospective study.
†Prospective clinical trial.
‡Eighteen different regimens of immunotherapy and/or chemotherapy were used.
§Median progression-free survival, 3.2 months.

RESULTS

Patient Characteristics

Forty-three patients with metastatic sarcomatoid RCC who received VEGF-targeted therapy were identified (Table 2). Patients received sunitinib (n = 21), sorafenib (n = 12), bevacizumab (n = 8), or the combination of sunitinib and bevacizumab (n = 2). The median age was 57 years, and 79% of patients were men. The median time from diagnosis to treatment was relatively short at 7 months, and 70% of patients had been diagnosed within 1 year from starting therapy. All patients had undergone prior nephrectomy, and 44% had received prior systemic therapy that consisted largely of cytokine-based regimens. Eighty-six percent of patients had a Karnofsky performance status (KPS) of 80% or greater. The majority had intermediate or poor risk group features according to different published criteria.[39,40] The most common sites of metastatic disease included lung, liver, and bone; of note, seven patients (16%) had brain metastases. The majority of patients had clear-cell RCC; two patients had papillary RCC; and eight patients (19%) had unclassified RCC. Additional immunohistochemical staining was performed for the 8 unclassified patient cases, but no additional diagnostic information was obtained to additionally subclassify them. Complete slides were available for re-review in 34 patients in whom sarcomatoid percentages

Table 2. Patient Characteristics

Characteristic	Patients No.	Patients %
Sex		
Male	34	79
Female	9	21
Age, years		
Median	57	
Range	32-84	
Time from diagnosis to treatment, months		
Median	7.0	
Range	0.2-84	
Prior nephrectomy	43	100
Prior systemic therapy	19	44
IL-2	11	26
IFN	8	19
Thalidomide	3	7
Karnofsky performance status		
100	5	12
90	17	40
80	15	35
≥ 70	6	14
MSKCC risk group[39]		
Favorable	8	19
Intermediate	30	70
Unfavorable	5	12
CCF TKI risk group[40]		
Favorable	9	21
Intermediate	12	28
Unfavorable	22	51
Metastatic site		
Lung	32	74
Liver	11	26
Bone	14	33
Brain	7	16
Histology		
Clear-cell	33	77
Papillary	1	2
Chromophobe	1	2
Unclassified	8	19
Sarcomatoid		
%		
Median	14	
Range	3-90	
< 10	11	32
10-20	10	29
21-49	4	12
≥ 50	9	26
Treatment		
Sunitinib	21	49
Sorafenib	12	28
Bevacizumab	8	19
Sunitinib + bevacizumab	2	5

Abbreviations: IL-2, interleukin-2; IFN, interferon; MSKCC, Memorial Sloan-Kettering Cancer Center; CCF TKI, Cleveland Clinic Foundation Tyrosine Kinase Inhibitor.

were estimated. The median number of slides reviewed for each patient case was eight (range, two to 17). The median percentage sarcomatoid was 14% (range, 3% to 90%), and 76% of patients had less than 50% sarcomatoid elements. Only primary tumor samples were reviewed. No additional sites, such as lymph nodes or metastatic deposits, were reviewed for sarcomatoid differentiation.

Clinical Outcome

The overall objective partial response (PR) rate was 19% (eight patients; Table 3). Stable disease (SD) was achieved in 21 patients (49%), and progressive disease was the best response in 14 patients (33%). Fifty-three percent of patients demonstrated some degree of tumor shrinkage, and the median tumor shrinkage was −2% (range, −85% to 127%). Of the patients who demonstrated a PR, the median time to response was 9.2 months (range, 5 to 19 months). At the time of analysis, 39 (91%) of 43 patients had progressed, and 25 (58%) of 43 had died. Median PFS was 5.3 months, and median OS was estimated at 11.8 months.

When responses were examined with respect to RCC histology, all PRs occurred in patients who had underlying clear-cell RCC (Table 3). The response rate of these patients was 24%, and a median PFS and OS of 6.0 and 13.1 months, respectively. The median tumor shrinkage of patients who had clear-cell histology was −5%, and 61% of these patients had some degree of tumor shrinkage. By comparison, in patients who had non–clear-cell histology, the median PFS and OS were 4.2 and 9.8 months, respectively; the median tumor shrinkage was 13.5% (range, −18% to 47%), and only 30% demonstrated any degree of tumor shrinkage. Because of the limit of small patient numbers, the differences in outcomes between clear-cell and non–clear-cell histologies were not statistically significant. There were no differences among any of the treatments received with respect to objective response, PFS, or OS in the total study population or in the subgroup of patients who had clear-cell tumors, although patients who received sunitinib therapy appeared to have a numerically higher PR rate compared with those who received other therapies (Table 3).

The impact of sarcomatoid differentiation was additionally assessed by analyzing the proportion of the tumor that contained sarcomatoid elements (Table 4). There were 33 patients who had clear-cell histology. They had a median of 10% sarcomatoid elements (range, 3% to 90%), and 62% had less than 20% sarcomatoid components. The 10 patients who had non–clear-cell histology had a higher percentage sarcomatoid (median, 40%; range, 5% to 80%), and only 25% had less than 20% sarcomatoid components. PRs were confined to patients who had less than 20% sarcomatoid elements ($P = .02$), and only 4 (22%) of 18 of these patients had a best response of progression compared with nine (56%) of 16 of the patients who had ≥ 20% sarcomatoid tumors. There was also some suggestion that patients who had less than 20% sarcomatoid elements experienced significantly more tumor reduction overall (median, 7% decrease *v* 10% increase; $P = .05$). The differences in PFS (6.8 *v* 4.3 months) and OS (14.9 *v* 8.6 months) favored the group that had less than 20% sarcomatoid elements, but the differences were not statistically significant.

To place the observed clinical outcomes in perspective, patients who had sarcomatoid RCC and clear-cell histology were matched to a separate group of patients who had nonsarcomatoid RCC and clear-cell histology who also received treatment with VEGF-targeted therapy (Table 5). Thirty-two pairs were matched for age, sex, treatment received, and prognostic risk group,[39] which was based on performance status, time from diagnosis to study entry, hemoglobin, corrected serum calcium, and lactate dehydrogenase. PFS was significantly longer in the patients who had nonsarcomatoid RCC (16.3 *v* 6.2 months; $P < .001$). Similarly, tumor shrinkage was significantly greater in patients who had nonsarcomatoid RCC than in the patients who had sarcomatoid elements (median, 32% *v* 5% decrease, respectively; $P = .005$). The objective response rate to therapy was

Table 3. Clinical Outcome to VEGF-Targeted Therapy According to Histologic Subtype and Treatment Received

	Outcome											
	PR		SD		PD		Tumor Shrinkage (%)		PFS (months)		OS (months)	
Histology and Treatment	No.	%	No.	%	No.	%	Median	Range	Median	95% CI	Median	95% CI
Histology												
Clear-cell	8	24	16	48	9	27	−5	−85-127	6.0	4.6 to 8.3	13.1	9.0 to 26.3
Unclassified	—	—	4	50	4	50	14	−18-44	4.2	1.0 to 8.3	9.8	2.1 to 11.8
Papillary	—	—	1	100	—	—	−10		8.2		19.9	
Chromophobe	—	—	—	—	1	100	47		1.0		2.3	
Total (N = 43)	8	19	21	49	14	33	−2.0	−85-127	5.3		11.8	
Treatment												
Sunitinib	6	29	9	43	6	29	−10	−58-47	5.3	4.1 to 8.3	11.8	7.4 to 26.3
Sorafenib	1	8	6	50	5	42	−9	−56-53	4.5	2.5 to 8.3	10.5	6.4 to 30.2
Bevacizumab	1	13	4	50	3	38	−1	−85-127	7.8	2.4 to 9.6	17.4*	
Sunitinib + bevacizumab	—	—	2	100	—	—	−12	−19-−5	NA	NA	NA	NA
Total (N = 43)	8	19	21	49	14	33	−2.0	−85-127	5.3		11.8	

Abbreviations: PFS, progression-free survival; OS, overall survival; PR, partial response; SD, stable disease; PD, progressive disease; NA, not applicable.
*Insufficient data to calculate 95% CI.

also greater in patients who did not have sarcomatoid differentiation (50% *v* 25%; $P = .02$).

DISCUSSION

Patients who have metastatic RCC with sarcomatoid differentiation can demonstrate objective responses and tumor shrinkage to VEGF-targeted therapy. These responses were less frequent than those seen in similar patients who did not have sarcomatoid differentiation, and they appeared worse on the basis of the percentage of sarcomatoid elements, which suggests that this histologic finding continues to be associated with worse outcomes in the modern treatment era.

In patients who had sarcomatoid RCC in this study, the clinical outcome to VEGF-targeted agents compares favorably with previous studies of chemotherapy or immunotherapy. In the largest published prospective clinical trial, Escudier et al[20] treated 23 patients who had sarcomatoid RCC with the combination of doxorubicin and ifosfamide and reported no objective responses and median PFS and OS of 2.2 and 3.9 months, respectively. Other recent reports have also examined VEGF-targeted therapy in sarcomatoid RCC. As part of a phase I trial, five patients who had sarcomatoid RCC were treated with the combination of sunitinib and gemcitabine. Two patients had a PR, two had SD, and one had PD as their best responses.[41] In another report, 15 patients who had predominately sarcomatoid RCC were treated with sorafenib after progression on gemcitabine plus doxorubicin. No responses were seen with gemcitabine and doxorubicin, but one PR (3 months) and four SDs (range, 3 to 9 months) were documented while patients received sorafenib.[42]

In addition, there was suggestion in this study that patients who had underlying clear-cell histology had better outcomes with anti-VEGF therapy compared with those who had non–clear-cell sarcomatoid metastatic RCC. Previous studies have found no association between histologic subtype and outcome in sarcomatoid metastatic RCC.[6,7,9,15] Type of therapy received may also influence outcome. Sunitinib is distinguished among VEGF-targeted therapies in RCC by a high objective response rate. The present study also identified sunitinib with the most robust objective response rate in patients who have sarcomatoid RCC.

A standardized method of calculating percentage of sarcomatoid elements is presented, which can be reproduced in future prospective trials. Additional collaboration to standardize the definition and calculation of percentage of sarcomatoid elements is needed. There are currently two ongoing, phase II clinical trials that utilize VEGF-targeted agents in sarcomatoid RCC: sunitinib plus gemcitabine in sarcomatoid and/or poor-risk patients who

Table 4. Patient Outcome in Relation to Percentage of Sarcomatoid Elements

	Outcome											
	PR		SD		PD		Tumor Shrinkage (%)		PFS (months)		OS (months)	
Sarcomatoid Element	No.	%	No.	%	No.	%	Median	Range	Median	95% CI	Median	95% CI
1%-20% (n = 18)	6	33	8	44	4	22	−7	−85-127	6.8	4.1 to 8.2	14.9	9.0 to 37.7
> 20% (n = 16)	0	0	7	44	9	56	10	−19-47	4.3	1.7 to 5.5	8.6	3.1 to 19.8
P	.02*		—		—		.05†		.78‡		.16‡	

Abbreviations: PFS, progression-free survival; OS, overall survival; PR, partial response; SD, stable disease; PD, progressive disease.
*Fisher's exact test for partial response *v* no partial response.
†Wilcoxon rank sum test.
‡Log-rank test.

Table 5. Clinical Outcomes in Matched Patients With the Presence or Absence of Sarcomatoid RCC

	Outcome									
	CR/PR*		SD		PD		Tumor Shrinkage (%)		PFS (months)	
Sarcomatoid Element	No.	%	No.	%	No.	%	Median	Range	Median	Range
Yes (n = 32)	8	25	15	47	9	28	−5	−85-127	6.2	4.6-9.0
No (n = 32)	16	50	13	41	3	9	−32	−100-70	16.3	11.5-19.0
P	.02†		—		—		.005‡		< .001§	

Abbreviations: PFS, progression-free survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*One patient without sarcomatoid elements had a complete response.
†McNemar's test for partial/complete response *v* no partial/complete response.
‡Wilcoxon signed rank test.
§Sign test.

have mRCC (NCT00556049), and capecitabine, gemcitabine, and bevacizumab in combination for patients who have sarcomatoid RCC (NCT00496587).

This study has several limitations. The retrospective nature of this review potentially introduces several biases. There was not uniform timing of post-treatment scans; as such, outcome measures, such as PFS, could be influenced. In addition, pathologic material was not available for re-review on all patients. Thus, a subset of patients was identified as sarcomatoid strictly from the original pathology report. Although all pathology was initially reviewed at a single institution, variability in the determination of the presence of sarcomatoid features is possible. In addition, although a consistent method to determine the percentage of sarcomatoid elements was applied during the subsequent expert review, only a mean of eight slides per patient were re-reviewed and, thus, may not have been entirely representative of the whole tumor. Finally, available pathology material was from nephrectomy specimens and not metastatic tissue, although response to therapy was determined on the basis of radiographic changes of metastatic sites.

VEGF-targeted therapy has clinical activity in patients who have metastatic RCC with sarcomatoid features, most notably in patients who have clear-cell histology and a low percentage of sarcomatoid elements. Additional prospective investigation to optimize treatment of patients who have sarcomatoid RCC is required.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Tarek M. Mekhail, Genentech (C), Sanofi-aventis (C), Imclone Systems Inc (C); Jorge A. Garcia, Wyeth (C), Pfizer Inc (C); Ronald M. Bukowski, Pfizer Inc (C), Bayer (C); Brian I. Rini, Pfizer Inc (C), Genentech Inc (C), Wyeth (C), Novartis (C) **Stock Ownership:** None **Honoraria:** Tarek M. Mekhail, Genentech Inc, Eli Lilly, Sanofi-aventis; Ronald M. Bukowski, Novartis, Genentech Inc, Pfizer Inc, Bayer, Wyeth, Onyx, Antigenics **Research Funding:** Tarek M. Mekhail, Pfizer Inc; Jorge A. Garcia, Genentech Inc, Pfizer Inc, Novartis inc, Wyeth; Ronald M. Bukowski, Pfizer Inc; Brian I. Rini, Pfizer Inc, Genentech Inc, Wyeth **Expert Testimony:** None **Other Remuneration:** None

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