VOLUME 27 · NUMBER 34 · DECEMBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Daniel Y.C. Heng, Wanling Xie, Meredith M. Regan, Mark A. Warren, Ali Reza Golshayan, Chakshu Sahi, Bernhard J. Eigl, J. Dean Ruether, Tina Cheng, Scott North, Peter Venner, Jennifer J. Knox, Kim N. Chi, Christian Kollmannsberger, David F. McDermott, William K. Oh, Michael B. Atkins, Ronald M. Bukowski, Brian I. Rini, and Toni K. Choueiri

From the Tom Baker Cancer Center, Calgary; Cross Cancer Institute, Edmonton, Alberta; Princess Margaret Hospital, Toronto, Ontario; British Columbia Cancer Agency, Vancouver, British Columbia, Canada; Harvard School of Public Health; Dana-Farber/Harvard Cancer Center Renal Cancer Program, Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, Boston, MA; Medical University of South Carolina, Charleston, SC; and Cleveland Clinic Taussig Cancer Institute, Cleveland, OH.

Submitted December 9, 2008; accepted June 18, 2009; published online ahead of print at www.jco.org on October 13, 2009.

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

Corresponding author: Daniel Y.C. Heng, MD, MPH, FRCPC, Department of Medical Oncology, Tom Baker Cancer Center, University of Calgary, 1331 29th St NW, Calgary, Alberta, Canada T2N 4N2; e-mail: daniel.heng@cancerboard.ab.ca.

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

0732-183X/09/2734-5794/$20.00

DOI: 10.1200/JCO.2008.21.4809

ABSTRACT

Purpose
There are no robust data on prognostic factors for overall survival (OS) in patients with metastatic renal cell carcinoma (RCC) treated with vascular endothelial growth factor (VEGF) –targeted therapy.

Methods
Baseline characteristics and outcomes on 645 patients with anti-VEGF therapy–naïve metastatic RCC were collected from three US and four Canadian cancer centers. Cox proportional hazards regression, followed by bootstrap validation, was used to identify independent prognostic factors for OS.

Results
The median OS for the whole cohort was 22 months (95% CI, 20.2 to 26.5 months), and the median follow-up was 24.5 months. Overall, 396, 200, and 49 patients were treated with sunitinib, sorafenib, and bevacizumab, respectively. Four of the five adverse prognostic factors according to the Memorial Sloan-Kettering Cancer Center (MSKCC) were independent predictors of short survival: hemoglobin less than the lower limit of normal ($P < .0001$), corrected calcium greater than the upper limit of normal (ULN; $P = .0006$), Karnofsky performance status less than 80% ($P < .0001$), and time from diagnosis to treatment of less than 1 year ($P = .01$). In addition, neutrophils greater than the ULN ($P < .0001$) and platelets greater than the ULN ($P = .01$) were independent adverse prognostic factors. Patients were segregated into three risk categories: the favorable-risk group (no prognostic factors; n = 133), in which median OS (mOS) was not reached and 2-year OS (2y OS) was 75%; the intermediate-risk group (one or two prognostic factors; n = 301), in which mOS was 27 months and 2y OS was 53%; and the poor-risk group (three to six prognostic factors; n = 152), in which mOS was 8.8 months and 2y OS was 7% (log-rank $P < .0001$). The C-index was 0.73.

Conclusion
This model validates components of the MSKCC model with the addition of platelet and neutrophil counts and can be incorporated into patient care and into clinical trials that use VEGF-targeted agents.

J Clin Oncol 27:5794-5799. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Metastatic renal cell carcinoma (RCC) portends a poor prognosis and is estimated to have caused 13,010 deaths in the United States in 2008.[1] Previously, immunotherapy agents, such as interleukin-2 and interferon alfa (IFN-α), were the only treatments available and demonstrated response rates of approximately 10% to 22%.[2-7] The biology underlying RCC has been elucidated, and agents that target relevant biologic pathways, including vascular endothelial growth factor (VEGF), have been investigated.[8] Agents such as sunitinib, sorafenib, and bevacizumab have revolutionized the treatment of RCC and have largely displaced immunotherapy as the first-line standard of care.[9-12] Sunitinib, sorafenib, and bevacizumab have been approved for use in North America and Europe.

In this era of VEGF-targeted therapies, new prognostic variables are required for purposes of

clinical trial design, patient counseling, and risk-directed therapy. Currently, the most widely used prognostic factor model is from the Memorial Sloan-Kettering Cancer Center (MSKCC), which examined 463 patients with metastatic RCC enrolled on clinical trials and treated with IFN-α.[13] Adverse prognostic factors on multivariable analysis included an interval from diagnosis to treatment of less than 1 year, Karnofsky performance status less than 80%, serum lactate dehydrogenase (LDH) greater than 1.5 times the upper limit of normal (ULN), corrected serum calcium greater than the ULN, and serum hemoglobin less than the lower limit of normal (LLN). The MSKCC criteria were validated and were additionally elaborated by an independent group at the Cleveland Clinic, which used a data set of 353 patients enrolled on clinical trials involving immunotherapy.[14] In addition to the MSKCC criteria, prior radiotherapy and greater than one site of metastases also had negative prognostic value.

It is important to note that these prognostic risk profiles are derived from the era of immunotherapy and are limited to a population of patients eligible for participation in immunotherapy clinical trials. It is unclear if the same prognostic factors previously reported are relevant to patients treated with VEGF-targeted therapy. Thus, new prognostic profiles with updated survival data are needed to reflect the current treatment paradigm for patients with metastatic RCC.

A retrospective, multicenter study to include consecutive patient series from seven different oncology treatment centers across North America was conducted to validate the existing MSKCC criteria and other prognostic factors previously found to be significant in recent studies. The goal was to create a simple clinical-prediction model that would be applicable to the general population of patients with metastatic RCC treated with VEGF-targeted therapy.

METHODS

Patient Population

Six hundred forty-five patients with metastatic RCC treated with sunitinib, sorafenib, or bevacizumab plus interferon between August 2004 to July 2008 were included in this study. Patient data were collected from consecutive patient series from Dana-Farber Cancer Institute (Boston, MA; n = 129), Cleveland Clinic Taussig Cancer Institute (Cleveland, OH; n = 113), Beth Israel Deaconess Medical Center (Boston, MA; n = 74), British Columbia Cancer Agency (including sites in Vancouver, Victoria, Kelowna, and Surrey, Canada; n = 100), Tom Baker Cancer Center (Calgary, Canada; n = 62), Cross Cancer Institute (Edmonton, Canada; n = 72) and the Princess Margaret Hospital (Toronto, Canada; n = 95). Patients from the Cleveland Clinic were studied previously as part of a prognostic factors study for progression-free survival[15]; however follow-up data has been updated significantly to allow for analysis of overall survival (OS; ie, different end point), and patients receiving axitinib were excluded.

Patient inclusion criteria comprised a diagnosis of metastatic RCC of any pathologic subtype with no prior anti-VEGF therapy. Patients received treatment with sunitinib, sorafenib, or bevacizumab. Patients who received prior immunotherapy (ie, received their targeted therapy as second-line treatment) also were included. Patients treated initially with temsirolimus (an inhibitor of mammalian target of rapamycin, or mTOR), an investigational agent (ie, PTK787, AZD2171, pazopanib), or an investigational combination (eg, bevacizumab plus erlotinib, bevacizumab plus sunitinib) were excluded.

Baseline demographic, clinical and laboratory data including those previously found to have prognostic value[13-16] were collected retrospectively on all patients by using uniform database templates to ensure consistent data collection. Laboratory values were standardized against institutional ULN and LLN values when appropriate. Outcome data on OS were collected from patient charts. This study received institutional review board approval from each participating center.

Statistical Analyses

The primary outcome was OS, which was defined as the time from initiation of VEGF-targeted therapy to death as a result of any cause or was censored at the date of last follow-up. Another outcome was time on VEGF-targeted therapy, which was defined as the time from initiation of sunitinib, sorafenib, or bevacizumab to the date of drug discontinuation or death or was censored at last follow-up. Distributions of OS and time on targeted therapy were estimated by using the Kaplan-Meier product-limit method; median and two-year OS along with 95% CIs were reported. Associations between OS and potential prognostic factors were assessed by using the log-rank test in univariable analysis. The Cox proportional hazards model was undertaken subsequently in multivariable analyses by using a step-wise procedure with a significance level of .15 for entering and removing variables. The proportionality assumption was assessed graphically by using plots of log(−log[survival]) versus log of survival time. The case deletion method was used to handle missing values in all explanatory variables. Once the prognostic factors were identified and the final model was formed, a risk-group variable was created by counting the number of unfavorable features presented for each patient. The predictive accuracy of the model was evaluated by the concordance index (C-index),[17] which is the area under the receiver operating characteristic curve

Table 1. Patient and Disease Characteristics (N = 645)

Variable	Total No. of Patients Evaluated (N = 645)	Patients	
		No.	%
Age at targeted therapy initiation, years	645		
Median		60	
Interquartile range		53-69	
Range		13-88	
Time from diagnosis to targeted therapy, years	645		
Median		1.4	
Interquartile range		0.3-4.3	
Range		0-31.6	
KPS, %	615		
Median		80	
Interquartile range		70-100	
Range		30-100	
Sex			
Male	645	473	73.3
Prior immunotherapy	645		
First-line anti-VEGF		431	66.8
Second-line anti-VEGF		214	33.2
Therapy	645		
Sunitinib		396	61.4
Sorafenib		200	31.0
Bevacizumab		49	7.6
Prior nephrectomy	645	532	82.5
More than one metastasis	645	489	75.8
Brain metastases present	645	53	8.2
Hemoglobin < LLN	612	336	54.9
Serum corrected calcium > ULN	601	68	11.3
Lactate dehydrogenase > ULN	544	78	14.3
Neutrophils > ULN	583	68	11.7
Platelets > ULN	607	115	18.9
Non–clear cell pathology	595	35	5.9
Sarcomatoid features	591	23	3.9

Abbreviations: KPS, Karnofsky performance status; VEGF, vascular endothelial growth factor; LLN, lower limit of normal; ULN, upper limit of normal.

for censored data, in which a value of 0.5 indicates no predictive discrimination, and a value of 1 represents a perfect ability to separate patients.

We also assessed the predictive performance of the final model by internal validation by using two-step bootstrap resampling procedures.[18] In the first step, 300 bootstrap samples were generated randomly with replacement from the original study population (N = 645). The stepwise Cox regression procedure was employed to each sample with the same selection criteria as the original modeling, described earlier in this Methods section. We then calculated the frequency of each variable that was included in the resulting models from the 300 bootstrap samples. Risk factors that were present in greater than 50% of the models were considered significant. In the second validation step, we validated parameter estimates of the final model. Three hundred bootstrap samples were generated randomly from the original study population for the final model. For each of the samples, we refit the Cox regression model by using the variables selected in the final model, and we calculated the regression parameters and hazard ratios. The means, standard deviations, and CIs were computed from the 300 samples and were compared to the model by using the original study population.

The C-index analysis was calculated by using the validation function of the R Design library (http://cran.r-project.org/web/packages/Design/index.html) with 500 bootstrap samples. This approach provides a bias-corrected estimate of prediction accuracy to protect against overfitting during stepwise regression. All other statistical analyses were undertaken by using SAS version 9 (SAS Institute, Cary, NC), and $P < .05$ (two sided) was considered statistically significant.

RESULTS

Patient Characteristics and Outcomes

Baseline characteristics are presented in Table 1. Overall, 396, 200, and 49 patients were treated with sunitinib, sorafenib, and bevacizumab, respectively. Two hundred fourteen patients (33.2%) had prior immunotherapy, and 532 patients (82.5%) had prior nephrectomy. At the time of analysis, 496 patients (76.9%) had discontinued their initial VEGF-targeted therapies, and 304 patients (47.1%) had died. The median follow-up time after treatment initiation was 24.5 months, and the median time on initial VEGF-targeted therapy was 8.8 months. Thirty-five percent of patients went on to receive another therapy during disease progression. The median OS for the entire cohort of 645 patients was 22 months (95% CI, 20.2 to 26.5 months; Fig 1), and the 2-year OS for the entire cohort was 47% (95% CI, 42% to 52%).

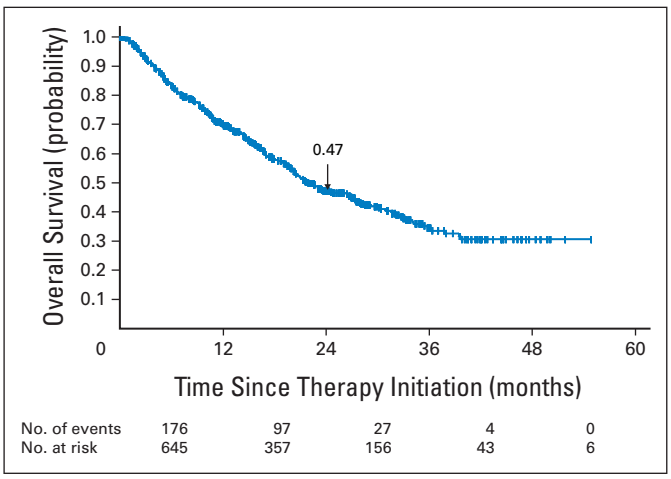

Fig 1. Overall survival probability according to time after therapy initiation.

Univariable Analysis

All 16 potential predictive covariates with their univariable analyses are presented in Table 2. Clinical features that were significantly associated with poor OS included a KPS less than 80%, no prior

Table 2. Univariate Analysis of Patient Demographic and Clinical Characteristics and Overall Survival

Parameter	No. of Patients Died	No. of Patients Total	Median Overall Survival (months)	Log-Rank *P*
Sex				.488
Male	221	473	22.6	
Female	83	172	21.0	
Age, years				.944
≥ 60	159	342	21.7	
< 60	145	303	23.0	
Nephrectomy				< .0001
Yes	234	532	27.0	
No	70	113	10.9	
Treatment				.764
Sunitinib	173	396	21.6	
Sorafenib	101	200	22.7	
Bevacizumab	30	49	21.3	
Prior immunotherapy				.726
First-line anti-VEGF	180	431	21.3	
Second-line anti-VEGF	124	214	22.7	
Anemia				< .0001
Yes	190	336	16.9	
No	98	276	39.4	
Hypercalcemia				< .0001
Yes	49	68	8.8	
No	234	533	26.8	
Neutrophilia				< .0001
Yes	50	68	5.9	
No	225	515	27.0	
Thrombocytosis				< .0001
Yes	74	115	10.4	
No	212	492	27.4	
Elevated LDH				.001
Yes	50	78	15.8	
No	206	466	26.3	
KPS, %				< .0001
< 80	110	163	9.4	
> 80	178	452	31.6	
No. of metastases				.125
> 1	241	489	21.1	
1	63	156	26.4	
Brain metastasis				.070
Yes	28	53	14.0	
No	276	592	22.7	
Histology				.015
Non–clear cell	20	35	16.8	
Clear cell	259	560	22.7	
Sarcomatoid features				.016
Yes	13	23	8.6	
No	263	568	22.7	
Time from diagnosis to treatment, years				< .0001
< 1	148	278	15.8	
> 1	156	367	30.9	

NOTE. Total number of patients = 645.
Abbreviations: VEGF, vascular endothelial growth factor; LDH, lactate dehydrogenase; KPS, Karnofsky performance status.

nephrectomy, and a time from initial diagnosis (including original localized disease) to treatment of less than 1 year. Laboratory features that were associated with poor OS included anemia, hypercalcemia, neutrophilia, thrombocytosis, and elevated LDH. Non–clear cell histology and the presence of sarcomatoid features on pathology also were associated with poor OS. Of note, there were no differences in OS when patients receiving VEGF-targeted therapy first- or second-line ($P = .726$) were compared or when patients receiving sunitinib, sorafenib, or bevacizumab ($P = .764$) were compared.

Multivariable Analysis

In the resulting Cox proportional hazards model (Table 3), four of the five adverse prognostic factors previously identified by MSKCC[13]—hemoglobin less than the LLN ($P < .0001$), serum corrected calcium greater than the ULN ($P = .0006$), Karnofsky performance status less than 80% ($P < .0001$) and time from initial diagnosis to initiation of therapy of less than 1 year ($P = .0098$)—were independent predictors of short survival. Additionally, absolute neutrophil count greater than ULN ($P < .0001$) and platelets greater than ULN ($P = .0121$) were independent adverse prognostic factors. None of the six variables violated the proportional hazards assumption.

According to these six prognostic factors, patients were segregated into three risk categories. In this study, patients with zero adverse factors were in the favorable-risk category (n = 133; 22.7%) in which a median OS was not reached and a 2-year OS was 75% (95% CI, 65% to 82%). Patients with one or two adverse factors were in the intermediate-risk category (n = 301; 51.4%), in which a median OS was 27 months and a 2-year OS was 53% (95% CI, 46% to 59%). Finally, those patients with three to six adverse factors were in the poor-risk category (n = 152; 25.9%), in which a median OS was 8.8 months and a 2-year OS was 7% (95% CI, 2% to 16%). The Kaplan-Meier curves depicting these three risk categories are shown in Figure 2.

Bootstrap Validation and Model Checking

The stepwise Cox regression procedure was employed with each of the 300 random bootstrap samples with the same selection criteria as the original modeling. The frequency of each variable that was included in the resulting models was very high (Appendix Table A1, online only). The regression parameters and hazard ratios produced from the 300 bootstrap samples (Table 4) were remarkably similar to the original model, which suggests excellent internal validation. The biased-corrected C-index of this model was 0.73 by a bootstrap procedure.

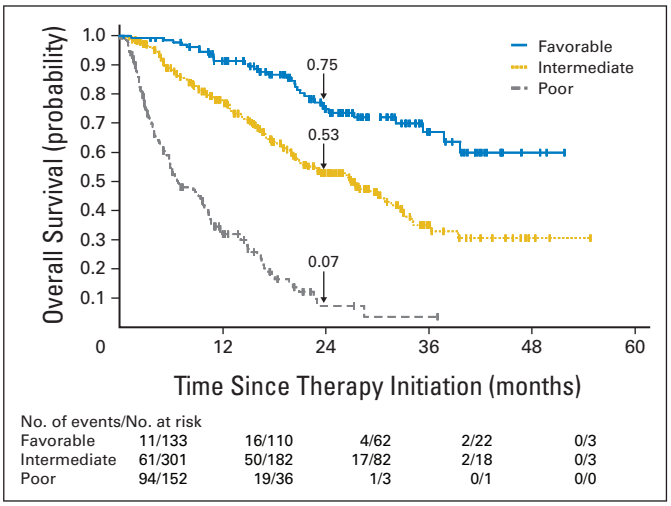

Fig 2. Overall survival probability according to time after therapy initiation and risk group.

Because of the clinical importance of the type of VEGF-targeted therapy used and whether it was used first- or second-line therapy, the model was evaluated in these specific patient populations separately. The C-indexes of the model with the six risk factors, when applied to these specific populations, ranged from 0.70 (patients on sorafenib) to 0.77 (patients on sunitinib). Additionally, the parameter estimates of each of the six variables after stratifying for the type of therapy and the line of therapy were similar to those of the original model (Appendix Tables A2 and A3, online only).

DISCUSSION

VEGF-targeted therapies have created a new environment for clinical trials development and patient care in patients with metastatic RCC. Contemporary prognostic models are required to better stratify patients in clinical trials, to provide relevant clinical information to patients receiving therapy, and to facilitate risk-directed treatment selection in clinical practice.

Table 3. Multivariable Analysis and Final Model

Parameter	Parameter Estimate ± SE	Hazard Ratio	95% CI	*P*
Clinical				
KPS < 80%	0.92 ± 0.14	2.51	1.92 to 3.29	< .0001
Time from diagnosis to treatment < 1 year	0.35 ± 0.13	1.42	1.09 to 1.84	.0098
Laboratory				
Hemoglobin < LLN	0.54 ± 0.14	1.72	1.31 to 2.26	.0001
Calcium > ULN	0.59 ± 0.17	1.81	1.29 to 2.53	.0006
Neutrophil count > ULN	0.88 ± 0.17	2.42	1.72 to 3.39	< .0001
Platelet count > ULN	0.40 ± 0.16	1.49	1.09 to 2.03	.0121

NOTE. Total number of patients = 564.
Abbreviations: SE, standard error; KPS, Karnofsky performance status; LLN, lower limit of normal; ULN, upper limit of normal.

Table 4. Bootstrap Parameter Means, Hazard Ratio Means, 95% CIs, and Bias-Corrected C-Index

Parameter	Parameter Bootstrap Mean	Hazard Ratio Bootstrap	
		Mean	95% CI
KPS < 80%	0.94265	2.594	1.86 to 3.33
Time from diagnosis to treatment < 1 year	0.36361	1.452	1.07 to 1.84
Hemoglobin < LLN	0.54652	1.744	1.27 to 2.22
Calcium > ULN	0.61659	1.893	1.11 to 2.68
Neutrophils > ULN	0.87723	2.459	1.42 to 3.49
Platelets > ULN	0.40522	1.524	0.99 to 2.06

NOTE. Bias-corrected C-index = .73.
Abbreviations: KPS, Karnofsky performance status; LLN, lower limit of normal; ULN, upper limit of normal.

The Cleveland Clinic developed a prognostic model by using 120 patients receiving sunitinib, sorafenib, axitinib, or bevacizumab on clinical trial. This single-institution, retrospective study found that an interval from diagnosis to treatment of less than 2 years, baseline corrected serum calcium less than 8.5 mg/dL or greater than 10 mg/dL, Eastern Cooperative Oncology Group performance status greater than 0, neutrophil count greater than 4.5 K/μL, and platelet count greater than 300 K/μL were all predictors of poor outcome.[15]

In another study, the outcome data from the phase III trial in which sunitinib was compared with IFN-α was used to derive a prognostic model for those treated with sunitinib alone (n = 375). A prognostic nomogram was created by using 11 factors, including corrected serum calcium, number of metastatic sites, hemoglobin, prior nephrectomy, presence of lung metastases, presence of liver metastases, Eastern Cooperative Oncology Group performance status, thrombocytosis, time from diagnosis to treatment, alkaline phosphatase, and LDH.[16]

These two studies and other previously published prognostic tools have been restricted to a clinical-trials population and/or to a single center.[15,16] Older prognostic models also were restricted to the immunotherapy-treated population.[13,14] Thus, a contemporary prognostic factor model that is applicable to all patients with metastatic RCC treated with VEGF-targeted therapy, including patients treated on or off clinical trials, is required.

The final model described in this study is composed of two clinical and four laboratory values that are readily available and that have been demonstrated to be associated with adverse outcomes. Karnofsky performance status, anemia, hypercalcemia, and a short time from diagnosis to treatment are factors that have been previously reported in the MSKCC criteria and may reflect increased tumor burden, aggressive tumor biology, and/or paraneoplastic processes.[13,14,19,20] Neutrophilia[21] and thrombocytosis[22,23] may be markers of inflammation related to the overproduction of cytokines as a result of increasing tumor burden or aggressive tumor biology. This six-factor model is associated with a C-index of 0.73. This is comparable to other published models in the era of targeted therapy, in which the C-index is 0.63.[16] However, it must be noted that the study designs are different, because the phase III trial-derived nomogram study focuses on PFS for patients receiving sunitinib,[16] whereas our study predicts OS across multiple agents.

The median OS of the entire patient cohort of this study (22 months), including each strata of patients with favorable (OS not reached), intermediate (OS, 27 months), and poor (OS, 8.8 months) prognoses is longer than that seen in previous studies in the era of immunotherapy. Although the factors in each model are not entirely the same, the MSKCC model[13] and the subsequent Cleveland Clinic Foundation extension and validation model[14] had the following median OS times, respectively: entire cohort (13 and 14.8 months), favorable-risk group (29.6 and 26 months), intermediate-risk group (13.8 and 14.4 months), and poor-risk group (4.9 and 7.3 months). These results are compatible with the improved efficacy of VEGF-targeted therapies when compared with immunotherapy in randomized, controlled trials.[9,11,12]

Factors that are traditionally included, such as elevated LDH levels and nephrectomy status, were not found informative in this model. Possible explanations include that the other covariates already in this model made LDH and nephrectomy status not statistically significant. Regarding LDH, additional explanations include missing values, use of a different cutoff point, and possible differences in the patient population regarding the incidence of LDH elevation compared with previous studies. Regarding nephrectomy, the large majority of patients included in this study already had a nephrectomy; thus, it may not be as clinically useful if included in the model. Other factors, such as creatinine clearance, presence of bone metastases, and prior radiotherapy, were not included, because this data was not collected.

Pathologic covariates, including non–clear cell histology[24-26] and sarcomatoid histology,[27] have been associated with adverse outcome. In our study, sarcomatoid histology ($P = .016$) and non–clear cell histology ($P = .015$) were associated with inferior OS. However, only a small percentage of patients had these adverse features in our cohort ($< 6\%$); because of the absence of a central pathology review, conclusions remain difficult to draw. Thus, these two parameters were not included in the final model.

The limitations to this study include that this is a retrospective analysis that has the associated issues of potential selection bias, incomplete data collection, and lack of pathology review. Attempts to address these concerns were made and included the use of consecutive patient sampling to reduce patient selection bias and several efforts to obtain complete patient information from medical records, provincial registries, and physician offices.

Additionally, this patient population was heterogeneous and included patients treated with sunitinib, sorafenib, and bevacizumab in either the first- or second-line setting. Although this assumes similar activity of the three agents, including their application as initial therapy or after cytokine failure, it enables this model to be applicable to a larger patient population. Of interest, there was no apparent difference in OS in patients treated with any of the targeted therapies, and there was no difference if patients were previously treated with immunotherapy or not. Including these variables in the multivariable model did not change the predictive value. This may be because of the use of second-, third-, and forth-line targeted therapies that may dilute any difference in OS attributable to one single agent. Furthermore, the model continued to perform well even when applied to these specific subgroups of patients, which emphasizes the general applicability of the model. This is in keeping with previous data on progression-free survival, which show that PFS is unaffected by targeted therapy administered as first- or second-line (median PFS, 14.7 months *v* 13.8 months; $P = .79$).[15] Although multiple factors may influence this outcome, these data suggest that the treatment approaches may be non–cross-resistant; thus, failure of immunotherapy does not influence the effect of VEGF-targeted therapy.

In summary, we present a prognostic model composed of six readily available clinical parameters that are able to stratify patients into favorable, intermediate, and poor prognosis groups. External validation is ongoing currently with other data sets. All of these factors have been found previously to be prognostic, and this study serves to validate components of and extend the MSKCC criteria in the age of targeted therapy.

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:** J. Dean Ruether, Pfizer (C), Bayer Pharmaceuticals (C), Novartis (C); Peter Venner, Pfizer (C), Wyeth (C), Novartis (C); David F. McDermott, Genentech (C), Wyeth (C), Novartis (C), Roche (C); Michael B. Atkins, Bayer Pharmaceuticals (C), Onyx (C), Genentech (C), AVEO Pharmaceuticals (C), Novartis (C); Ronald M. Bukowski, Pfizer (C), Bayer Pharmaceuticals (C), Novartis (C), Wyeth (C), Genentech (C); Brian I. Rini, Bayer Pharmaceuticals (C), Onyx (C), Wyeth (C), Pfizer (C), Genentech (C); Toni K. Choueiri, Novartis (C), Genentech (C), Abbott Laboratories (C), GlaxoSmithKline (C) **Stock Ownership:** None **Honoraria:** Daniel Y.C. Heng, Bayer Pharmaceuticals, Wyeth, Pfizer; J. Dean Ruether, Pfizer; Scott North, Pfizer, Wyeth, Bayer Pharmaceuticals; Peter Venner, Pfizer, Wyeth, Novartis; Jennifer J. Knox, Pfizer, Novartis, Bayer Pharmaceuticals; Ronald M. Bukowski, Bayer Pharmaceuticals, Pfizer, Novartis, Wyeth, Genentech; Brian I. Rini, Bayer Pharmaceuticals, Onyx, Wyeth, Pfizer, Genentech; Toni K. Choueiri, Pfizer, Bayer Pharmaceuticals, Onyx **Research Funding:** Tina Cheng, Pfizer; Peter Venner, Wyeth, Novartis, Pfizer; Jennifer J. Knox, Pfizer, Bayer Pharmaceuticals; Michael B. Atkins, Novartis, Bayer Pharmaceuticals; Ronald M. Bukowski, Pfizer, Genentech, Bayer Pharmaceuticals, Bristol-Myers Squibb **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Daniel Y.C. Heng, Toni K. Choueiri
Financial support: Daniel Y.C. Heng, Ronald M. Bukowski, Brian I. Rini
Administrative support: Daniel Y.C. Heng, Toni K. Choueiri
Provision of study materials or patients: Daniel Y.C. Heng, Bernhard J. Eigl, J. Dean Ruether, Tina Cheng, Scott North, Peter Venner, Jennifer J. Knox, Kim N. Chi, Christian Kollmannsberger, David F. McDermott, William K. Oh, Michael B. Atkins, Ronald M. Bukowski, Brian I. Rini, Toni K. Choueiri
Collection and assembly of data: Daniel Y.C. Heng, Mark A. Warren, Ali Reza Golshayan, Chakshu Sahi, Tina Cheng, Scott North, Toni K. Choueiri
Data analysis and interpretation: Daniel Y.C. Heng, Wanling Xie, Meredith M. Regan, Michael B. Atkins, Ronald M. Bukowski, Brian I. Rini, Toni K. Choueiri
Manuscript writing: Daniel Y.C. Heng, Wanling Xie, Meredith M. Regan, Scott North, Michael B. Atkins, Ronald M. Bukowski, Brian I. Rini, Toni K. Choueiri
Final approval of manuscript: Daniel Y.C. Heng, Wanling Xie, Meredith M. Regan, Mark A. Warren, Ali Reza Golshayan, Chakshu Sahi, Bernhard J. Eigl, J. Dean Ruether, Tina Cheng, Scott North, Peter Venner, Jennifer J. Knox, Kim N. Chi, Christian Kollmannsberger, David F. McDermott, William K. Oh, Michael B. Atkins, Ronald M. Bukowski, Brian I. Rini, Toni K. Choueiri

REFERENCES

1. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2008. CA Cancer J Clin 58:71-96, 2008

2. McDermott DF, Regan MM, Clark JI, et al: Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. J Clin Oncol 23:133-141, 2005

3. Yang JC, Sherry RM, Steinberg SM, et al: Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. J Clin Oncol 21:3127-3132, 2003

4. Negrier S, Escudier B, Lasset C, et al: Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal cell carcinoma: Groupe Francais D'Immunotherapie. N Engl J Med 338:1272-1278, 1998

5. Negrier S, Perol D, Ravaud A, et al: Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: Results of a randomized controlled trial. Cancer 110:2468-2477, 2007

6. Coppin C, Porzsolt F, Awa A, et al: Immunotherapy for advanced renal cell cancer. Cochrane Database Syst Rev 2:CD001425, 2005

7. Coppin C, Le L, Porzsolt F, et al: Targeted therapy for advanced renal cell carcinoma. Cochrane Database Syst Rev 2:CD006017, 2008

8. Cohen HT, McGovern FJ: Renal cell carcinoma. N Engl J Med 353:2477-2490, 2005

9. Motzer RJ, Hutson TE, Tomczak P, et al: Sunitinib versus interferon alfa in metastatic renal cell carcinoma. N Engl J Med 356:115-124, 2007

10. Escudier B, Eisen T, Stadler WM, et al: Sorafenib in advanced clear cell renal cell carcinoma. N Engl J Med 356:125-134, 2007

11. Escudier B, Pluzanska A, Koralewski P, et al: Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: A randomised, double-blind phase III trial. Lancet 370:2103-2111, 2007

12. Rini BI, Halabi S, Rosenberg JE, et al: CALGB 90206: A phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in metastatic renal cell carcinoma. Presented at the Genitourinary Cancers Symposium, San Francisco, CA, February 14-16, 2008

13. Motzer RJ, Bacik J, Murphy BA, et al: Interferon alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 20:289-296, 2002

14. Mekhail TM, Abou-Jawde RM, Boumerhi G, et al: Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. J Clin Oncol 23:832-841, 2005

15. Choueiri TK, Garcia JA, Elson P, et al: Clinical factors associated with outcome in patients with metastatic clear cell renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. Cancer 110:543-550, 2007

16. Motzer RJ, Bukowski RM, Figlin RA, et al: Prognostic nomogram for sunitinib in patients with metastatic renal cell carcinoma. Cancer 113:1552-1558, 2008

17. Harrell FE Jr, Lee KL, Mark DB: Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15:361-387, 1996

18. Chen CH, George SL: The bootstrap and identification of prognostic factors via Cox's proportional hazards regression model. Stat Med 4:39-46, 1985

19. Kim HL, Belldegrun AS, Freitas DG, et al: Paraneoplastic signs and symptoms of renal cell carcinoma: Implications for prognosis. J Urol 170:1742-1746, 2003

20. Sandhu DP, Munson KW, Harrop JS, et al: Humoral hypercalcaemia in renal carcinoma due to parathyroid hormone related protein. Br J Urol 72:848-850, 1993

21. Donskov F, von der Maase H: Impact of immune parameters on long-term survival in metastatic renal cell carcinoma. J Clin Oncol 24:1997-2005, 2006

22. Suppiah R, Shaheen PE, Elson P, et al: Thrombocytosis as a prognostic factor for survival in patients with metastatic renal cell carcinoma. Cancer 107:1793-1800, 2006

23. Hollen CW, Henthorn J, Koziol JA, et al: Serum interleukin-6 levels in patients with thrombocytosis. Leuk Lymphoma 8:235-241, 1992

24. Choueiri TK, Plantade A, Elson P, et al: Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. J Clin Oncol 26:127-131, 2008

25. Motzer RJ, Bacik J, Mariani T, et al: Treatment outcome and survival associated with metastatic renal cell carcinoma of non–clear-cell histology. J Clin Oncol 20:2376-2381, 2002

26. Cheville JC, Lohse CM, Zincke H, et al: Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Am J Surg Pathol 27:612-624, 2003

27. Golshayan AR, George S, Heng DY, et al: Metastatic sarcomatoid renal cell carcinoma treated with vascular endothelial growth factor–targeted therapy. J Clin Oncol 27:235-241, 2009