Outcome of Patients With Metastatic Sarcomatoid Renal Cell Carcinoma: Results From the International Metastatic Renal Cell Carcinoma Database Consortium

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Abstract

Outcome and prognosis of metastatic sarcomatoid renal cell carcinoma (sRCC) in the targeted therapy era are not well described. In this retrospective series of 230 patients with metastatic sRCC, we examined the role of anti–vascular endothelial growth factor (VEGF) agents as a treatment option. The validity of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model in patients with metastatic sRCC was confirmed. Sarcomatoid histology was found to be an independent factor for adverse prognosis.

Background: Sarcomatoid renal cell carcinoma is associated with poor prognosis. Data regarding outcome in the targeted therapy era are lacking. **Patients and Methods:** Clinical, prognostic, and treatment parameters in metastatic renal cell carcinoma patients with and without sarcomatoid histology treated with targeted therapy were retrospectively analyzed. **Results:** Two thousand two hundred eighty-six patients were identified (sRCC: n = 230 and non-sRCC: n = 2056). sRCC patients had significantly worse IMDC prognostic criteria compared with non-sRCC (11% vs. 19% favorable risk; 49% vs. 57% intermediate risk, and 40% vs. 24% poor risk; $P < .0001$). Time from original diagnosis to relapse (excluding synchronous metastatic disease) was shorter in the sRCC group (18.8 vs. 42.9 months; $P < .0001$). There was no significant difference in the incidence of central nervous system metastases (6%-8%) or underlying clear cell histology (87%-88%). More than 93% of patients received VEGF inhibitors as first-line therapy; objective response was less common in sRCC whereas primary refractory disease was more common (21% vs. 26% and 43% vs. 21%; $P < .0001$, for both). sRCC patients had significantly less use of second- ($P = .018$)

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and third-line ($P < .0001$) systemic therapy. The median progression-free survival (PFS)/overall survival (OS) was 4.5/10.4 months in sRCC patients and 7.8/22.5 months in non-sRCC patients ($P < .0001$ for both). Sarcomatoid histology was associated with a significantly worse PFS and OS after adjusting for individual IMDC risk factors in multivariable analysis (hazard ratio, 1.5; $P < .0001$ for both). **Conclusion:** Patients with sRCC have a shorter time to relapse, worse baseline prognostic criteria, and worse clinical outcome with targeted therapy. Additional insight into the biology of sRCC is needed to develop alternative therapeutics.

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Introduction

Renal cell carcinoma (RCC) is a histologically heterogeneous disease.[1] Clear cell carcinoma comprises the most common subtype (approximately 70%-80% of all cases) followed by other less common histologies such as papillary (10%-15%), chromophobe (3%-5%), medullary and unclassified (4%-6%).[2] Each histologic type arises from different parts of the nephron and possesses distinct genetic profiles, clinical characteristics, and prognosis.[2]

Sarcomatoid is a term used to describe morphologic changes within an RCC tumor similar to sarcomas—like elongated, spindle-shaped cells, high cellularity and cellular atypia, and can be recognized in association with every histologic type of RCC. According to the 2004 World Health Organization classification of renal tumors of adults,[2] RCCs with sarcomatoid differentiation are not considered a distinct subtype and they are classified according to the underlying histology; when no epithelial elements can be recognized, those tumors are categorized as unclassified.[3,4] Sarcomatoid differentiation is observed in approximately 5% to 10% of all RCC and it is believed to represent a clonal expansion of tumor cells with greater accumulation of genetic alterations and cellular dedifferentiation.[5-7] Clinically, tumors with sarcomatoid changes carry a poor prognosis with rapid tumor growth, high rates of metastasis at the time of diagnosis, poor response to historical treatment, and shorter overall survival (OS).[8-14]

This study was performed by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). The aim of the current study was to identify patients with metastatic RCC with sarcomatoid differentiation (sRCC) and compare their clinical characteristics, prognostic factors, and targeted therapy treatment outcomes with patients with metastatic RCC without sarcomatoid features (non-sRCC). Additionally, the applicability of the IMDC prognostic model to patients with sRCC was investigated.

Patients and Methods

Study Population

The IMDC database includes cancer centers from Canada, the United States, South Korea, Japan, Denmark, Greece, and Singapore. Eighteen academic institutions that participate in the IMDC contributed consecutive series of patients with metastatic RCC treated with targeted therapy. Data were retrospectively collected from August 15, 2008, until January 28, 2013. At the time of the analysis, the database contained information about sarcomatoid histology for 2286 patients. Two hundred thirty patients were found to have tumors with sarcomatoid differentiation, whereas 2056 patients did not have sarcomatoid features identified. All centers obtained local institutional review board approval before collecting data for this large retrospective study. Baseline patient characteristics included demographic and clinicopathologic characteristics, and laboratory data as described in the development study of IMDC or Heng et al model.[15] Survival data were retrospectively collected from medical charts and electronic records. Standardized data collection templates were used to ensure consistent data collection across all study centers. Most patients in the study received standard-of-care treatment; a small proportion of patients received treatment in the context of a clinical trial.

Statistical Analyses

The primary end point of our study was to compare the overall response rate (ORR) to anti−vascular endothelial growth factor (VEGF) agents and the progression-free survival (PFS) and OS between metastatic RCC patients with and without sarcomatoid differentiation. PFS was measured in months and was defined as the time from initiation of treatment to documented disease progression according to investigator-assessed Response Evaluation Criteria in Solid Tumors 1.1 (RECIST),[16] treatment cessation, death, or censored at last follow-up. OS was measured in months and was defined as the time between initiation of treatment and death or censored at last follow-up. The secondary end point of this analysis was to confirm the validity of the IMDC (Heng et al)[15] prognostic model in patients with metastatic sRCC. The end points were compared using Kaplan−Meier curves. Proportional hazards regression was used to adjust censored outcomes to known predictors of poor OS according to the IMDC criteria: anemia, thrombocytosis, neutrophilia, hypercalcemia, time from diagnosis to treatment interval < 1 year, and Karnofsky Performance Status < 80%.

Results

Baseline Characteristics

The study cohort included 2286 patients with metastatic RCC (Table 1). Overall, 230 patients (10%) had sRCC and 2056 (90%) had non-sRCC. The mean age at diagnosis was 58 years in both groups ($P = .2617$) and most patients had underlying clear cell histology (88% vs. 87%; $P = .5372$). Patients with sRCC had a significantly worse IMDC prognostic score (11% vs. 19% favorable, 49% vs. 57% intermediate, and 40% vs. 24% poor; $P < .0001$) and significantly higher Furman nuclear grade (2% vs. 4% grade 1, 5% vs. 30% grade 2, 17% vs. 46% grade 3, and 21% vs. 76% grade 4; $P < .0001$) compared with their non-sRCC counterparts. Both groups included similar numbers of patients with > 1 site of metastatic disease (73% for both groups; $P = .9786$), and there was no

Table 1 Patient Characteristics

Characteristic	Nonsarcomatoid, n = 2056[a]	Sarcomatoid, n = 230[a]	*P*
Mean Age at Onset of Metastatic Disease, Years	59	58	.2617
Heng Prognostic Score			<.0001
Favorable	336 (19%)	20 (11%)	
Intermediate	995 (57%)	88 (49%)	
Poor	417 (24%)	73 (40%)	
Greater Than 1 Metastatic Site			.9786
Yes	1494 (73%)	167 (73%)	
No	557 (27%)	62 (27%)	
Brain Metastases			.3035
Yes	165 (8%)	14 (6%)	
No	1878 (92%)	214 (94%)	
Underlying Clear Cell Histology			.5372
Yes	1766 (88%)	195 (87%)	
No	239 (12%)	30 (13%)	
Fuhrman Nuclear Grade			<.0001
1	53 (4%)	3 (2%)	
2	430 (30%)	9 (5%)	
3	661 (46%)	33 (17%)	
4	302 (21%)	145 (76%)	
First-Line Targeted Therapy			
Sunitinib	1449 (71%)	180 (78%)	
Sorafenib	410 (20%)	32 (14%)	
Axitinib	4 (<1%)	0 (0%)	
Bevacizumab	88 (4%)	4 (2%)	
Temsirolimus	46 (2%)	9 (4%)	
Pazopanib	36 (2%)	0 (0%)	
Everolimus	15 (1%)	5 (2%)	
Tivozanib	3 (<1%)	0 (0%)	
Use of Second-Line Therapy[b]			.0172
Yes	929 (45%)	85 (37%)	
No	1127 (55%)	145 (63%)	
Use of Third-Line Therapy[b]			.0004
Yes	335 (16%)	17 (7%)	
No	1721 (84%)	213 (93%)	
Time from Original Diagnosis to Relapse (Excluding de Novo Metastatic Disease)	42.9 Months (n = 970)	18.8 Months (n = 70)	<.0001
Best Response			<.0001
CR	10 (1%)	3 (3%)	
PR	198 (25%)	17 (18%)	
SD	408 (52%)	34 (36%)	
PD	162 (21%)	40 (43%)	

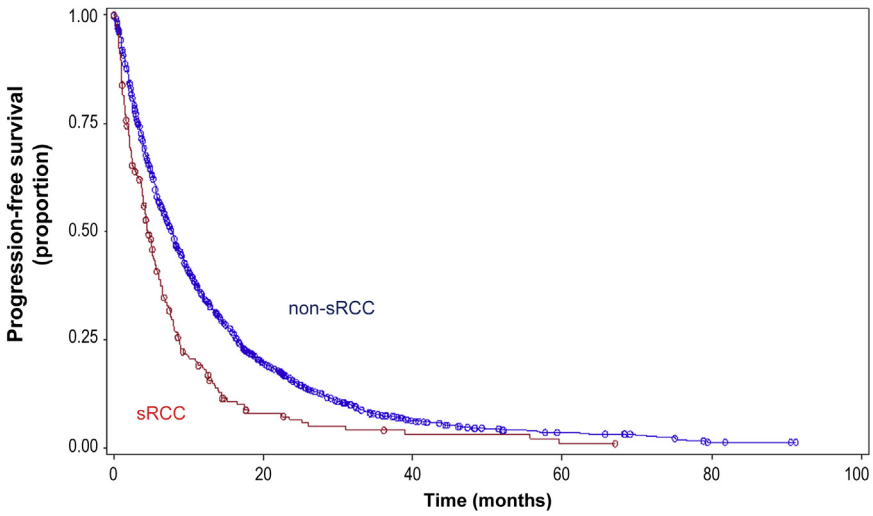
Data are presented as n (%) except where otherwise stated.
[a]Raw numbers might not add up to total because of missing data.
[b]Experimental therapy on clinical trials of investigational drugs not included.

significant difference detected in the incidence of brain metastasis between the 2 groups (6% vs. 8%; $P = .3035$). Regarding the patients who underwent curative-intent nephrectomy, the time from surgery to disease relapse was significantly shorter for the sRCC group (n = 70) compared with the non-sRCC patients (n = 970; 18.8 months vs. 42.9 months; $P < .0001$).

Comparison of sRCC With Non-sRCC in Treatment Response and OS

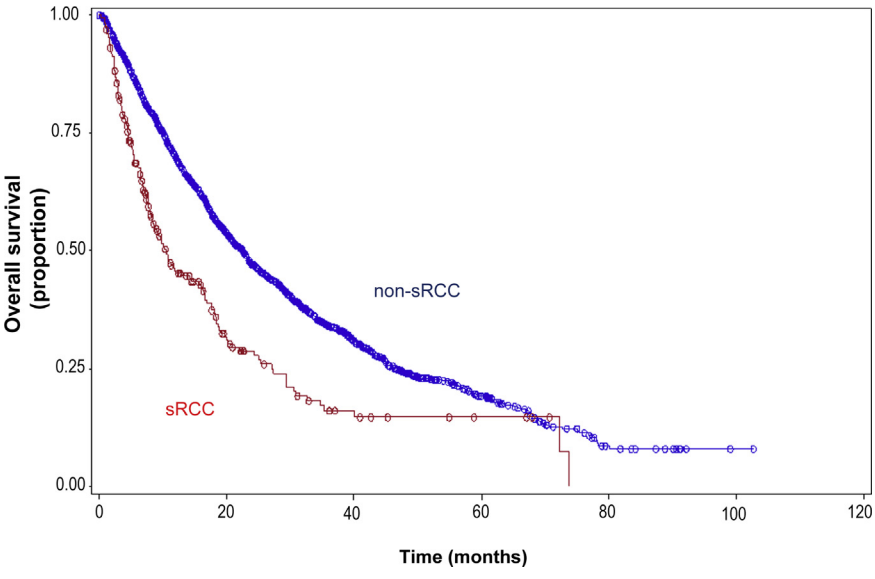
All patients received targeted therapy with most patients in both groups treated with anti-VEGF as first-line treatment (93% vs. 97%). Sunitinib was the most common first-line agent used (78% vs. 71%), followed by sorafenib (14% vs. 20%), axitinib

Figure 1 Progression-Free Survival of Patients With Sarcomatoid Renal Cell Carcinoma (sRCC; n = 224) Versus Nonsarcomatoid Metastatic Renal Cell Carcinoma (Non-sRCC; n = 2028; 4.5 Vs. 7.8 Months; $P < .0001$)



(0% vs. < 1%), bevacizumab (2% vs. 4%), pazopanib (0% vs. 2%), and tivozanib (0% vs. < 1%; Table 1). None of the patients received first-line cytokine therapy and only a minority of patients were treated with temsirolimus (4% vs. 2%) or everolimus (2% vs. 1%). The ORR was significantly different between the 2 groups. An objective response was achieved in 20% of patients in the sRCC group versus 26% in the non-sRCC group, with a complete response (CR) rate of 3% versus 1% and a partial response (PR) rate of 18% versus 25%, respectively ($P < .0001$). Additionally, fewer patients in the sRCC group had stable disease (SD; 36% vs. 52%) and more patients in the sRCC group had primary refractory disease (43% vs. 21%; $P < .0001$). In terms of subsequent treatments on disease progression, patients with sRCC were less likely to receive second- (37% vs. 45%; $P = .0172$) and third-line treatment (7% vs. 16%; $P = .0004$) compared with the non-sRCC group. Furthermore, there was a significant difference in PFS (4.5 months vs. 7.8 months; $P < .0001$) and OS (10.4 months vs. 22.5 months; $P < .0001$) between the 2 groups (Figures 1 and 2).

Figure 2 Overall Survival of Patients With Sarcomatoid Renal Cell Carcinoma (sRCC; n = 230) Versus Nonsarcomatoid Metastatic Renal Cell Carcinoma (Non-sRCC; n = 2055; 10.4 Vs. 22.5 Months; $P < .0001$)



International Metastatic Renal Cell Carcinoma Database Consortium Risk Model for sRCC

The validity of the IMDC model as a prognostic tool for PFS and OS in patients with sRCC was investigated (Tables 2 and 3). Data regarding the presence or absence of the 6 predefined IMDC risk criteria were collected from all sRCC patients with complete data (n = 181). Twenty (11%), 88 (49%), and 73 (40%) sRCC patients were assigned to favorable, intermediate, and poor risk groups, respectively. Among all sRCC patients, the median OS was 10.4 months and the median OS differed significantly between the 3 groups. The median OS for the favorable risk group was 29 months, 14 months for the intermediate group, and 5.5 months for the poor risk group ($P < .0001$; Figure 3). Sarcomatoid histology was associated with a significantly worse PFS (hazard ratio [HR], 1.51; 95% confidence interval [CI], 1.25-1.83; $P < .0001$) and OS (HR, 1.51; 95% CI, 1.28-1.79; $P < .0001$) after adjusting for the individual IMDC risk factors in multivariable analysis.

Discussion

The present analysis demonstrated that patients with metastatic RCC with sarcomatoid histologic features present with less favorable histologic and clinical characteristics, such as higher Furman nuclear grade, IMDC prognostic score, and shorter time from nephrectomy to disease relapse. Further, anti-VEGF agents might play a role in the treatment of metastatic sRCC; however the response to this treatment is limited with a worse ORR, PFS, and OS than was observed in the non-sRCC patients in the IMDC cohort. Finally, the applicability and validity of the IMDC risk groups applied to patients with metastatic sRCC allowed differentiation between PFS and OS outcomes.

The efficacy of anti-VEGF agents in the treatment of metastatic sRCC remains unknown. In a previous study[9] the retrospective experience from 43 metastatic sRCC patients treated with anti-VEGF therapy was reported. A PFS and OS of 5.3 and 11.8 months, respectively, was shown; results that are consistent with the current report. A greater percentage of sarcomatoid differentiation (20% or less vs. > 20%) was also found to be an adverse prognostic factor in terms of response to treatment (PR, 33% vs. 0%; SD, 44% vs. 44%; progressive disease, 22% vs. 56%; $P = .02$) and possibly PFS and OS (PFS of 6.8 months vs. 4.3 months; $P = .78$; and OS of 14.9 months and 8.6 months; $P = .16$, respectively). Another retrospective study of 63 patients[10] that examined the role of cytokines, targeted therapies, or systemic treatment in patients with metastatic sRCC showed similar results for the group treated with anti-VEGF agents. Of the 34 patients who received sunitinib as first-line or second-line therapy, 22 responded to treatment (ORR, 65%) with a PFS of 4.4 months (95% CI, 2.2-6.7). One patient (3%) achieved CR, 4 patients (12%) PR, 17 patients (50%) SD, and 12 patients (35%) did not respond to treatment. Moreover, a recent phase II study of sunitinib in patients with non-clear cell RCC,[17] allowed patients with clear cell histology and > 20% sarcomatoid differentiation to enroll. Although the number of patients with sRCC was small (n = 7), less than half of the patients responded (n = 3) and the median PFS was dismal (1.4 months), confirming the poor response and prognosis of sRCC patients. Finally, another study[14] that examined the role of sorafenib in 9 patients whose disease had progressed during systemic chemotherapy with doxorubicin and gemcitabine showed only 1 partial remission and a median time to progression (TTP) of 10.9 months.

Table 2 Multivariable Analysis of International Metastatic Renal Cell Carcinoma Database Consortium Risk Factors for Progression-Free Survival

Risk Factor	Parameter Estimate	HR (95% CI)	*P*
Sarcomatoid Histology	0.41	1.51 (1.28-1.79)	<.0001
KPS <80%	0.45	1.57 (1.40-1.76)	<.0001
Diagnosis to Treatment Interval <1 Year	0.19	1.21 (1.10-1.34)	.0002
High Calcium	0.22	1.25 (1.06-1.47)	.0086
Low Hemoglobin	0.32	1.37 (1.24-1.52)	<.0001
Neutrophilia	0.32	1.38 (1.19-1.59)	<.0001
Thrombocytosis	0.16	1.17 (1.03-1.34)	.0204

Abbreviations: HR = hazard ratio; KPS = Karnofsky performance status.

Table 3 Multivariable Analysis of International Metastatic Renal Cell Carcinoma Database Consortium Risk Factors for Overall Survival

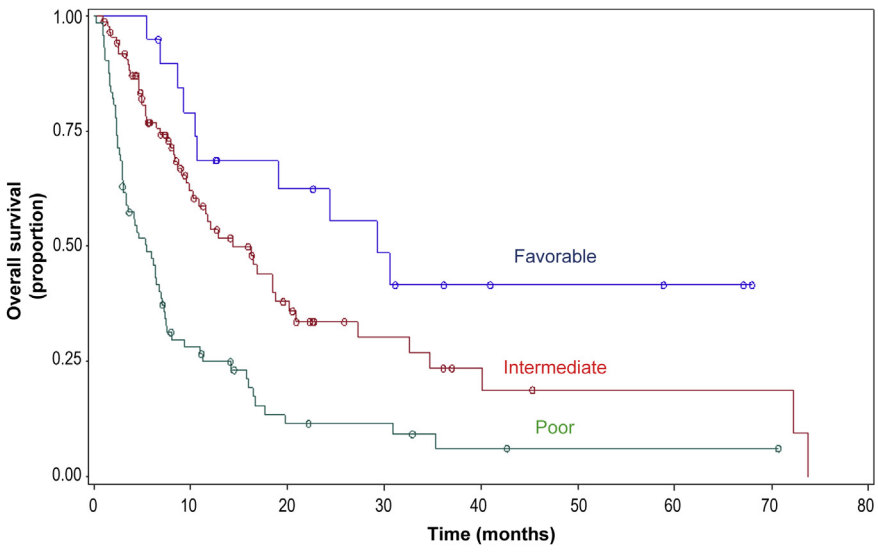
Risk Factor	Parameter Estimate	HR (95% CI)	*P*
Sarcomatoid Histology	0.41	1.51 (1.25-1.83)	<.0001
KPS <80%	0.77	2.16 (1.91-2.46)	<.0001
Diagnosis to Treatment Interval <1 Year	0.18	1.19 (1.06-1.34)	.0030
High Calcium	0.56	1.75 (1.47-2.09)	<.0001
Low Hemoglobin	0.42	1.52 (1.34-1.72)	<.0001
Neutrophilia	0.54	1.71 (1.46-2.00)	<.0001
Thrombocytosis	0.36	1.44 (1.24-1.67)	<.0001

Abbreviations: HR = hazard ratio; KPS = Karnofsky performance status.

Systemic chemotherapy has also been studied in the treatment of metastatic sRCC with poor results. The most common agent used is doxorubicin in combination with either gemcitabine[11,12] or ifosfamide.[13] Even though there are reports of favorable outcomes with combination chemotherapy of doxorubicin and gemcitabine,[18] a recent phase II study (Eastern Cooperative Oncology Group 8802) showed a response rate of 16% with a median PFS and OS of 3.5 months and 8.8 months, respectively.[12] The combination of doxorubicin with ifosfamide did not yield any meaningful clinical results.[13] Finally, chemotherapy has been used in combination with anti-VEGF agents. An interim analysis of an ongoing trial of gemcitabine and sunitinib[19] showed a partial response rate of 33% in patients with sRCC (n = 9), with a TTP of 4.6 months. Two additional ongoing trials are also exploring the combination of systemic chemotherapy with anti-VEGF agents, the first using a combination of gemcitabine and sunitinib (NCT01164228) and the second using a combination of gemcitabine and capecitabine with bevacizumab (NCT00496587).

The retrospective nature of this study leads to several limitations, such as missing data and selection bias. Standard data collection templates were used by all participating institutions;

Figure 3 Application of the International Metastatic Renal Cell Carcinoma Database Consortium Risk Criteria in the Sarcomatoid Renal Cell Carcinoma—Segregated 3 Risk Groups With Favorable (n = 20), Intermediate (n = 88), and Poor Risk (n = 73) Profiles in Prognostication of Overall Survival (Median: Favorable, 29 Months; Intermediate, 14 Months; Poor, 5.5 Months; $P < .0001$)



however, it is possible that some data were not documented accurately. In addition, the lack of central review of the pathology specimens might have resulted in misclassification of sRCC and discrepancy of tumor grading among different institutions. Furthermore, the percentage of sarcomatoid differentiation in each specimen was not reported. It is also unknown if the specimens were reviewed by the same pathologist within each contributing institution, in which case it would confer a higher level of uniformity. Finally, there was no central radiologic review to determine disease progression based on RECIST; as a result it is possible that some inconsistency might exist in the capture of PFS between the different institutions.

Conclusion

Despite the tremendous progress in the treatment of metastatic RCC with VEGF inhibitors, the prognosis of sRCC remains poor. Anti-VEGF agents remain a reasonable option for the treatment of sRCC despite the lower ORR, PFS, and OS of this group. For sRCC patients, IMDC risk factors were found to be independent prognostic factors for risk of death. More studies are needed to better understand the biology and to further define the optimal treatment of this unfavorable histologic variant.

Clinical Practice Points

- Patients with sRCC tend to present with worse histologic and clinical characteristics.
- Anti-VEGF agents remain a reasonable treatment option for metastatic sRCC despite the poor response to treatment and overall prognosis.
- The IMDC prognostic model can be applied to patients with sRCC and can accurately predict their outcomes.
- Sarcomatoid histology is an independent factor for poor prognosis.

Disclosure

Toni K. Choueiri has received research funding from Pfizer and has an advisory role at Aveo, Bayer, Genentech, GlaxoSmithKline, Novartis, and Pfizer. Jae-Lyun Lee has received honoraria from Bayer, Novartis, and Pfizer, and has received research funding from Bayer. Jennifer J. Knox has been a consultant and has played an advisory role at Aveo and has received research funding from Pfizer. Georg A. Bjarnason has been a consultant and has played an advisory role at Pfizer and has received honoraria and research funding from Pfizer. Lori A. Wood has been a consultant and has played an advisory role at Pfizer and has received research funding from Pfizer, Novartis, and GlaxoSmithKline. Frede Donskov has received research funding from Novartis and GlaxoSmithKline. Daniel Y. Heng is a consultant and has an advisory role at Bayer/Onyx, Novartis, and Pfizer. Brian I. Rini has an advisory role at Pfizer and has received research funding from Pfizer. The remaining authors have stated that they have no conflicts of interest.

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