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# Prognostic factors for survival in 1059 patients treated with sunitinib for metastatic renal cell carcinoma

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**Background:** Prognostic factors for progression-free survival (PFS), overall survival (OS), and long-term OS ( $\geq 30$  months) were investigated in sunitinib-treated patients with metastatic renal cell carcinoma (RCC).

**Methods:** Data were pooled from 1059 patients in six trials. Baseline variables, including ethnicity, were analysed for prognostic significance by Cox proportional-hazards model.

**Results:** Median PFS and OS were 9.7 and 23.4 months, respectively. Multivariate analysis of PFS and OS identified independent predictors, including ethnic origin, Eastern Cooperative Oncology Group performance status, time from diagnosis to treatment, prior cytokine use, haemoglobin, lactate dehydrogenase, corrected calcium, neutrophils, platelets, and bone metastases (OS only). Characteristics of long-term survivors ( $n = 215$ , 20%) differed from those of non-long-term survivors; independent predictors of long-term OS included ethnic origin, bone metastases, and corrected calcium. There were no differences in PFS (10.5 vs 7.2 months;  $P = 0.1006$ ) or OS (23.8 vs 21.4 months;  $P = 0.2135$ ) in white vs Asian patients; however, there were significant differences in PFS (10.5 vs 5.7 months;  $P < 0.001$ ) and OS (23.8 vs 17.4 months;  $P = 0.0319$ ) in white vs non-white, non-Asian patients.

**Conclusion:** These analyses identified risk factors to survival with sunitinib, including potential ethnic-based differences, and validated risk factors previously reported in advanced RCC.

Sunitinib is an orally administered, multi-targeted inhibitor of receptors for vascular endothelial growth factor (VEGF), platelet-derived growth factor, and other tyrosine kinases (Chow and Eckhardt, 2007). Sunitinib demonstrated efficacy in patients with metastatic renal cell carcinoma (RCC) who progressed on cytokine therapy (Motzer *et al*, 2006a, b), and was the first targeted agent to show benefit compared with cytokine therapy in treatment-naïve patients with metastatic RCC (Motzer *et al*, 2009). In a randomised phase III trial, sunitinib demonstrated superior efficacy to

interferon (IFN)- $\alpha$  as first-line metastatic RCC therapy with a median progression-free survival (PFS) of 11 vs 5 months ( $P < 0.001$ ), respectively, (Motzer *et al*, 2009). In addition, median overall survival (OS) with sunitinib was  $> 2$  years (Motzer *et al*, 2009), establishing sunitinib as a reference standard of care. As such, new tyrosine kinase inhibitors (TKIs), as well as novel combinations, should be compared with sunitinib in phase III trials. Accordingly, identification of prognostic factors is important in clinical trial design and interpretation.

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Here, we report a retrospective analysis of prognostic factors for PFS and OS in 1059 metastatic RCC patients treated with sunitinib in six clinical trials (Motzer *et al*, 2006a, b, 2009, 2012; Escudier *et al*, 2009; Barrios *et al*, 2012). The features studied and compared include those reported in the Memorial Sloan-Kettering Cancer Center (MSKCC) model (which was developed in the era before targeted therapy; Motzer *et al*, 2002), as well as a similar model recently reported by Heng *et al* (2009), which was developed using a database of patients treated with a variety of VEGF-targeted drugs.

We explored ethnic-based differences in baseline characteristics and survival, as there have been differences in outcome and tolerability reported to sunitinib by ethnicity (Hong *et al*, 2009; Lee *et al*, 2009; Tomita *et al*, 2010). We identified a group of patients with long-term OS, defined as OS of  $\geq 30$  months, and examined pretreatment features in this cohort of patients. An *ad hoc* analysis of ethnic-based differences in tolerability was also conducted.

## MATERIALS AND METHODS

**Patients.** The population comprised patients aged  $\geq 18$  years with the following eligibility criteria: histologically confirmed metastatic RCC, evidence of measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST; Therasse *et al*, 2000), no known presence of brain metastases, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (or Karnofsky performance status  $\geq 70$  in one trial; Motzer *et al*, 2012), and adequate organ function.

**Study design and treatments.** This retrospective analysis investigated prognostic factors for PFS, OS, and long-term OS using pooled data from 1059 patients treated with sunitinib in six prospective trials for advanced RCC (Motzer *et al*, 2006a, b, 2009, 2012; Escudier *et al*, 2009; Barrios *et al*, 2012). Sunitinib was administered orally at a starting dose of either 50 mg per day for 4 consecutive weeks followed by 2 weeks off treatment in repeated 6-week cycles (schedule 4/2;  $n = 690$ ; 65%) or 37.5 mg per day on a continuous once-daily dosing schedule ( $n = 369$ ; 35%). Treatment continued until disease progression, lack of clinical benefit, unacceptable toxicity, or withdrawal of consent.

The studies were run in accordance with the International Conference on Harmonization Good Clinical Practice guidelines (or the Declaration of Helsinki) and applicable local regulatory requirements and laws, and approved by the institutional review boards or independent ethics committees of each participating centre (ClinicalTrials.gov: NCT00267748, NCT00137423, NCT00083889, NCT00077974, NCT00054886, NCT00338884).

**Statistical methods.** A multivariate Cox regression model was used to analyse potential baseline prognostic variables for PFS, OS, and long-term OS (i.e., OS  $\geq 30$  months). Previously identified prognostic factors, including those in the MSKCC and Heng *et al* risk models (Motzer *et al*, 2002; Heng *et al*, 2009), were investigated. Each variable was investigated by univariate and then multivariate analysis, using a stepwise algorithm, in which factors with  $P < 0.2$  by Wald  $\chi^2$  test were included in the multivariate analysis. Further elimination was applied within the multivariate analysis to identify variables significant at  $P < 0.05$ .

Median PFS and OS were estimated by Brookmeyer and Crowley method and compared between subgroups using a Wald  $\chi^2$  test. Tumour response was investigator-assessed by RECIST on schedules specified for each trial (initially every 4–6 weeks, increasing to every 8–12 weeks after approximately 6 months). Progression-free survival was defined as the time from the start of treatment or random assignment to tumour progression or death owing to any cause, and OS was defined as the time from the start of treatment or random assignment to death owing to any cause.

Within the ethnic subanalyses, baseline characteristics were separately compared between white patients vs Asian patients and vs non-white, non-Asian patients using either a Fisher's exact test, *t*-test, or Wilcoxon rank-sum test. Multivariate analyses of ethnic differences in PFS and OS were conducted using the Brookmeyer and Crowley method to estimate median values and a two-sided unstratified log-rank test to compare subgroups.

Baseline characteristics were compared between patients with and without long-term OS by either a Pearson or Mantel-Haenszel  $\chi^2$  test (with Fisher's exact test used when sample size requirements for the  $\chi^2$  test were not met).

An *ad hoc* analysis of ethnic-based differences in the occurrence of treatment-emergent adverse events (AEs) was conducted. AEs were recorded regularly in each trial and graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 3.0 (version 2.0 in one trial; Motzer *et al*, 2006a). Patient subgroups were compared using Fisher's exact test.

## RESULTS

**Patients, treatment, and outcome.** The majority of the 1059 sunitinib-treated patients were men (70%) and the median age was 60 years (Table 1). Eighty-three percent were white, 7% were

Table 1. Baseline patient characteristics

Characteristic	Sunitinib (n = 1059)
Median (range) age, years	60 (24–87)
Male/female, %	70/30
<b>Ethnic origin, %</b>	
White	83
Non-white	13
Missing	4
<b>ECOG PS, %</b>	
0	61
1	37
2	2
<b>Risk factors based on published MSKCC data, %<sup>a</sup></b>	
0 (favourable)	39
1–2 (intermediate)	39
$\geq 3$ (poor)	4
Missing	17
<b>Histology, %</b>	
Clear cell	97
Other	3
Missing	<1
Prior nephrectomy, % <sup>b</sup>	79
<b>Sites of metastasis, %</b>	
Lung	77
Liver	23
Bone	29

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; MSKCC = Memorial Sloan-Kettering Cancer Center.  
<sup>a</sup>Includes low serum haemoglobin level; elevated corrected serum calcium level; elevated serum lactate dehydrogenase level; poor performance status; and interval of <1 year between diagnosis and sunitinib treatment (Motzer *et al*, 2002).  
<sup>b</sup>Nephrectomy status is missing for 57 patients (4%).

**Table 2.** Baseline characteristics of white, Asian, and non-white, non-Asian patients

Characteristic	White (n = 884)	Asian (n = 70)	Non-white, non-Asian (n = 65)	P-value <sup>a</sup>	
				White vs Asian	White vs non-white, non-Asian
Median (range) age, years	61 (24–87)	61 (24–78)	57 (39–83)	0.218	0.003
Male/female, %	70/30	69/31	75/25	0.893	0.4
<b>ECOG PS, %</b>					
0	60	59	71	0.819	0.096
1	38	40	28		
2	2	1	2		
<b>Risk factors based on published MSKCC data, %<sup>b</sup></b>					
0 (favourable)	44	10	35	<0.001	0.233
1–2 (intermediate)	40	47	45		
≥3 (poor)	4	3	9		
Missing	12	40	11		
<b>Histology, %</b>					
Clear cell	93	99	85	0.079	0.046
Other	7	1	14		
Missing	<1	0	2		
Mean (range) time since initial diagnosis, years	2.5 (0.0–28.3)	2.2 (0.0–16.0)	1.9 (0.0–17.3)	0.498	0.211
Prior nephrectomy, % <sup>c</sup>	83	24	68	<0.001	0.05
Prior cytokine use, % <sup>c</sup>	25	23	14	0.671	0.037
<b>Sites of metastasis, %</b>					
Lung	79	71	71	0.178	0.213
Liver	24	10	22	0.007	0.763
Bone	30	26	23	0.5	0.321

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; MSKCC = Memorial Sloan-Kettering Cancer Center.

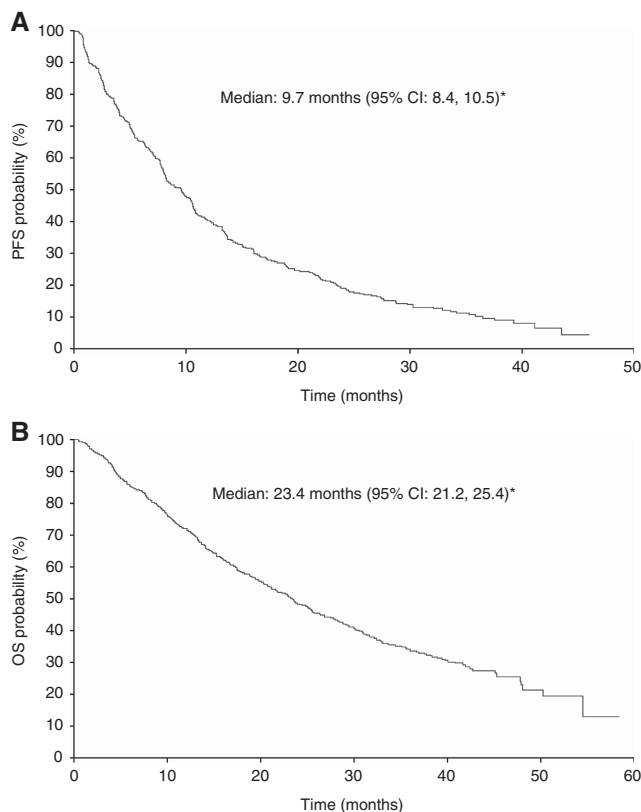
<sup>a</sup>P-values were calculated using Fisher's exact test (gender, sites of metastasis, histology, prior nephrectomy, prior cytokine use), t-test (age, time since initial diagnosis), and Wilcoxon rank-sum test (risk factors based on published MSKCC data, ECOG performance status).

<sup>b</sup>Includes low serum haemoglobin level; elevated corrected serum calcium level; elevated serum lactate dehydrogenase level; poor performance status; and interval of <1 year between diagnosis and sunitinib treatment (Motzer *et al*, 2002).

<sup>c</sup>Nephrectomy status is missing for 34 patients (4%) in the white group, 15 patients (21%) in the Asian group, and 7 patients (11%) in the non-white, non-Asian group; prior cytokine use missing for 1 patient (<1%) in the white group.

Asian, and 6% were non-white, non-Asian (e.g., black or Hispanic patients).

Age, gender, and performance status were similar between white and Asian patients (Table 2); however, more white patients compared with Asian patients had prior nephrectomy (83% vs 24%;  $P < 0.001$ ) and liver metastases at baseline (24% vs 10%;  $P = 0.007$ ). White patients compared with non-white, non-Asian patients (Table 2) were older (61 vs 57 years, respectively;  $P = 0.003$ ) and had higher rates of prior nephrectomy (83% vs 68%;  $P = 0.05$ ) and cytokine use (25% vs 14%;  $P = 0.037$ ), respectively. The reason for the lower than expected nephrectomy rate in the Asian population is unknown.



\*Based on the Brookmeyer and Crowley method.

**Figure 1.** Kaplan–Meier curves of (A) PFS and (B) OS in all patients.

Sunitinib was administered in either the first-line ( $n = 783$ ; 74%) or cytokine-refractory ( $n = 276$ ; 26%) setting. Median PFS and OS in all 1059 patients were 9.7 months (95% CI, 8.4–10.5 months) and 23.4 months (95% CI, 21.2–25.4 months), respectively (Figure 1).

**Prognostic factors for PFS and OS with sunitinib.** The following factors, identified with  $P < 0.2$  by univariate analysis, were subsequently included in the multivariate analysis (even if they were nonsignificant (NS) for PFS and/or OS): ECOG performance status, baseline lactate dehydrogenase, baseline haemoglobin, baseline-corrected calcium, time from diagnosis to treatment (all from the MSKCC prognostic model; Motzer *et al*, 2002), and also: age (NS for PFS/OS), ethnic origin, prior radiation (NS for PFS), baseline platelets, liver metastases (NS for PFS), lung metastases (NS for PFS), bone metastases, baseline alkaline phosphatase, baseline neutrophils, body mass index (BMI; overweight), body surface area (NS for PFS), prior medications (NS for PFS/OS), systolic blood pressure, and prior cytokine use.

The multivariate analysis identified 9 and 10 independent predictors for PFS and OS, respectively, (Table 3), including ethnic origin for both PFS and OS, and bone metastases for OS only (Figure 2). For example, white patients had a superior PFS to non-white patients with a median of 10.5 months (95% CI, 9.7–10.9 months) vs 6.6 months (5.4–7.8 months), respectively, (hazard ratio (HR), 0.598; 95% CI, 0.459–0.781;  $P = 0.0002$ ; Table 3).

There were no statistically significant differences in PFS or OS in white patients compared with Asian patients, irrespective of the first-line or cytokine-refractory treatment setting, although PFS was numerically longer in white patients (Table 4). However, there were significant differences in PFS and OS in white patients compared with non-white, non-Asian patients. In white patients,

Table 3. Final multivariate analysis of baseline characteristics predictive for PFS and OS with sunitinib

Variable	PFS					OS				
	Median, months <sup>a</sup>	95% CI	HR	95% CI	P-value <sup>b</sup>	Median, months <sup>a</sup>	95% CI	HR	95% CI	P-value <sup>b</sup>
<b>Ethnic origin</b>										
White	10.5	9.7–10.9	0.598	0.459–0.781	0.0002	23.8	21.8–26.2	0.730	0.535–0.996	0.0474
Non-white	6.6	5.4–7.8				18.3	14.7–25.5			
<b>ECOG PS<sup>c</sup></b>										
≥1	7.4	5.4–8.4	1.250	1.043–1.498	0.0159	14.1	13.0–16.3	1.505	1.218–1.859	0.0002
0	10.7	10.0–11.7				30.2	26.4–32.9			
<b>Time from diagnosis to treatment<sup>c</sup></b>										
≥1 year	11.8	10.6–13.7	0.814	0.680–0.975	0.0252	31.0	27.8–35.5	0.666	0.541–0.820	0.0001
<1 year	7.4	6.4–8.1				16.7	14.8–19.5			
<b>Bone metastases</b>										
Yes	—	—	—	—	NS	16.1	14.0–18.2	1.535	1.250–1.886	<0.0001
No						27.8	24.4–30.9			
<b>Baseline Hgb<sup>c</sup></b>										
≤LLN	6.5	5.1–7.8	1.384	1.144–1.675	0.0008	13.7	12.5–16.2	1.548	1.245–1.925	<0.0001
>LLN	11.1	10.7–12.6				30.9	28.2–34.2			
<b>Baseline LDH<sup>c</sup></b>										
>1.5 × ULN	4.1	2.8–6.9	1.664	1.201–2.305	0.0022	10.0	5.1–15.3	1.571	1.103–2.238	0.0123
≤1.5 × ULN	10.5	9.5–10.8				25.0	23.0–28.0			
<b>Baseline-corrected Ca<sup>c</sup></b>										
>10 mg dl <sup>-1</sup>	5.1	4.0–7.6	1.374	1.080–1.747	0.0096	10.9	9.6–14.0	2.208	1.722–2.832	<0.0001
≤10 mg dl <sup>-1</sup>	10.6	9.7–10.9				26.9	24.4–30.1			
<b>Baseline neutrophils</b>										
≤ULN	10.6	9.6–10.9	0.629	0.483–0.821	0.0006	25.1	23.0–28.2	0.681	0.508–0.915	0.0107
>ULN	3.4	2.7–6.4				11.7	6.6–13.7			
<b>Baseline platelets</b>										
≤ULN	10.7	10.0–11.3	0.607	0.469–0.785	0.0001	26.8	24.4–30.0	0.670	0.505–0.889	0.0055
>ULN	4.1	3.3–5.4				10.1	8.0–13.1			
<b>Prior cytokine</b>										
Yes	8.3	7.8–9.7	1.342	1.085–1.659	0.0066	19.1	15.8–24.0	1.387	1.094–1.759	0.0068
No	10.0	9.0–10.7				24.4	22.3–27.8			

Abbreviations: Ca = calcium; ECOG PS = Eastern Cooperative Oncology Group performance status; Hgb = haemoglobin; LDH = lactate dehydrogenase. For binary variables, a hazard ratio (HR) < 1 equates to risk reduction for the first category and a HR > 1 equates to risk reduction for the second category.

<sup>a</sup>On the basis of Brookmeyer and Crowley method.

<sup>b</sup>Wald  $\chi^2$  test.

<sup>c</sup>Risk factor included in the MSKCC prognostic model (Motzer *et al*, 2002).

median PFS was 10.5 months (95% CI, 9.7–10.9 months) vs 5.7 months (95% CI, 5.1–9.7) in non-white, non-Asian patients (HR, 0.575; 95% CI, 0.435–0.761;  $P < 0.001$ ); similarly, median OS was 23.8 months (95% CI, 21.8–26.2 months) vs 17.4 months (95% CI, 12.1–23.6 months), respectively (HR, 0.701; 95% CI, 0.506–0.972;  $P = 0.0319$ ).

**Prognostic factors for long-term OS with sunitinib.** Overall, 215 patients (20%) survived  $\geq 30$  months with sunitinib. Baseline characteristics differed between long-term survivors and

other patients (Table 5), including risk status based on MSKCC prognostic criteria (Motzer *et al*, 2002;  $P < 0.0001$ ). For example, 70% of the long-term survivors had favourable risk features compared with 31% of non-long-term survivors; in contrast, 42% and 5% of the non-long-term survivors had intermediate and poor risk features compared with 28% and 0% of long-term survivors, respectively. The proportion of patients without prior cytokine therapy was significantly higher among long-term compared with non-long-term survivors (79% vs 71%, respectively;  $P = 0.0170$ ), although previously treated patients also had long-term survival on sunitinib.

Independent prognostic factors were identified by multivariate analysis in patients with long-term OS (Table 6) and included ethnic origin, baseline bone metastases, and baseline-corrected calcium. For example, amongst this subgroup of long-term survivors, those without baseline bone metastases had a median OS of 54.5 months (95% CI, 47.8 months to not reached) compared with 42.7 months (95% CI, 37.5 months to not reached) for those with bone metastases (HR, 2.337; 95% CI, 1.275–4.285;  $P=0.0061$ ).

**Ethnic-based differences in tolerability.** Although many common treatment-emergent AEs occurred at similar rates regardless of ethnicity, there were significant ethnic-based differences in almost half of all such events (Table 7). The majority of differences occurred between white and Asian patients. For example, white patients experienced more nausea (55% vs 40%), dysgeusia (41% vs 26%), and decreased appetite (36% vs 17%), compared with Asian

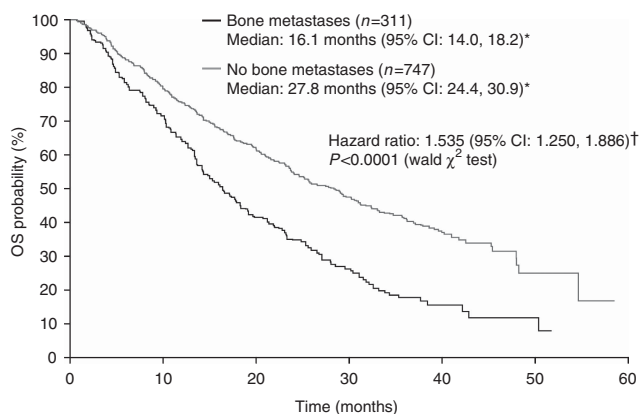
patients, respectively, who experienced more hand-foot syndrome (28% vs 70%) and mucosal inflammation (26% vs 40%; all  $P<0.05$ ). Compared with non-white, non-Asian patients, white patients experienced significantly more dyspepsia (33% vs 18%) and stomatitis (30% vs 14%; both  $P<0.05$ ). Tolerability was similar regardless of first-line or cytokine-refractory treatment setting (Supplementary Tables 1 and 2).

**DISCUSSION**

This retrospective analysis conducted in 1059 patients with metastatic RCC identified pretreatment clinical features that were associated with shorter survival to sunitinib. In addition, we identified a cohort of patients with a relatively long-term survival.

The pretreatment clinical features associated with sunitinib outcome are consistent with those previously reported in the MSKCC model (Motzer *et al*, 2002) and by Heng *et al* (2009); the latter obtained using data from patients outside clinical trials in a real-world setting. Small differences between factors identified previously in MSKCC analyses (Motzer *et al*, 2002) or more recently Heng *et al* (2009) and Choueiri *et al* (2007) in series comprising mixed targeted agents (sunitinib, sorafenib, bevacizumab (Choueiri *et al*, 2007; Heng *et al*, 2009), and axitinib (Choueiri *et al*, 2007)) likely represent a more select patient population and methodological differences. The commonality between factors suggests that these are not specific for a given treatment. Instead, these factors reflect a more aggressive underlying RCC biology.

The importance of these factors as associated with a shorter OS was demonstrated in the Cox proportional-hazards analysis performed for the phase III trial of sunitinib vs IFN. The analyses encompassed pretreatment clinical features plus the treatment arms as variables (Motzer *et al*, 2009). Although treatment was an independent variable, with sunitinib significantly better than IFN



\*Based on the Brookmeyer and Crowley method.  
†Based on the Cox proportional-hazards model.

Figure 2. Kaplan–Meier curve of OS by the presence/absence of bone metastases (multivariate analysis).

Table 4. Multivariate analysis of ethnic differences in PFS and OS with sunitinib

Ethnic variable	PFS					OS				
	Median, months <sup>a</sup>	95% CI	HR	95% CI	P-value <sup>b</sup>	Median, months <sup>a</sup>	95% CI	HR	95% CI	P-value <sup>b</sup>
<b>All patients</b>										
White	10.5	9.7–10.9	0.780	0.579–1.050	0.1006	23.8	21.8–26.2	0.793	0.550–1.143	0.2135
Asian	7.2	5.3–8.8				21.4	15.1–37.0			
White	10.5	9.7–10.9	0.575	0.435–0.761	<0.001	23.8	21.8–26.2	0.701	0.506–0.972	0.0319
Non-white, non-Asian	5.7	5.1–9.7				17.4	12.1–23.6			
<b>First-line patients only</b>										
White	10.7	9.8–11.2	0.820	0.590–1.139	0.2346	25.1	22.9–28.3	0.765	0.508–1.154	0.2007
Asian	7.2	5.4–11.1				17.4	15.1–38.4			
White	10.7	9.8–11.2	0.578	0.426–0.784	<0.001	25.1	22.9–28.3	0.717	0.500–1.030	0.0707
Non-white, non-Asian	6.6	5.1–9.8				20.3	12.6–33.0			
<b>Cytokine-refractory patients only</b>										
White	8.4	7.9–10.8	0.523	0.255–1.072	0.0709	19.1	14.5–25.1	0.765	0.337–1.738	0.5226
Asian	5.3	3.4–8.8				21.4	10.1–32.0			
White	8.4	7.9–10.8	0.482	0.235–0.990	0.0418	19.1	14.5–25.1	0.505	0.234–1.091	0.0763
Non-white, non-Asian	5.5	3.0–10.6				12.1	9.9–17.6			

Note: For binary variables, a hazard ratio (HR) < 1 equates to risk reduction for the first category and a HR > 1 equates to risk reduction for the second category.

<sup>a</sup>On the basis of Brookmeyer and Crowley method.

<sup>b</sup>Two-sided unstratified log-rank test.



Table 5. Baseline characteristics of patients with long-term OS (i.e., OS  $\geq$  30 months)

Characteristic	Long-term OS (n = 215)	Non-long-term OS (n = 844)	P-value
<b>Ethnic origin, %</b>			
White	94	81	0.0002 <sup>a</sup>
Non-white	6	15	
Missing	0	5	
<b>Risk factors based on published MSKCC data, %<sup>b</sup></b>			
0 (favourable)	70	31	<0.0001 <sup>c</sup>
1–2 (intermediate)	28	42	
$\geq$ 3 (poor)	0	5	
Missing	1	21	
<b>ECOG PS, %<sup>d</sup></b>			
0	75	58	<0.0001 <sup>c</sup>
1	25	40	
2	0	3	
<b>Prior nephrectomy, %</b>			
Yes	96	74	<0.0001 <sup>a</sup>
No	4	19	
Missing	0	7	
<b>Prior cytokine, %</b>			
Yes	21	29	0.0170 <sup>a</sup>
No	79	71	
Missing	0	<1	
<b>Baseline Hgb, %<sup>d</sup></b>			
$\leq$ LLN	22	44	<0.0001 <sup>a</sup>
> LLN	78	56	
Missing	0	<1	
<b>Baseline LDH, %<sup>d</sup></b>			
> 1.5 $\times$ ULN	3	7	0.0078 <sup>a</sup>
$\leq$ 1.5 $\times$ ULN	96	78	
Missing	1	15	
<b>Baseline-corrected Ca, %<sup>d</sup></b>			
> 10 mg dl <sup>-1</sup>	5	19	<0.0001 <sup>a</sup>
$\leq$ 10 mg dl <sup>-1</sup>	95	80	
Missing	0	1	
<b>Baseline neutrophils, %</b>			
$\leq$ ULN	97	78	<0.0001 <sup>e</sup>
> ULN	2	12	
Missing	1	10	
<b>Baseline platelets, %</b>			
$\leq$ ULN	96	80	<0.0001 <sup>a</sup>
> ULN	4	19	
Missing	0	<1	

Abbreviations: Ca = calcium; ECOG PS = Eastern Cooperative Oncology Group performance status; Hgb = haemoglobin; LDH = lactate dehydrogenase.

<sup>a</sup>Pearson  $\chi^2$  test for general association.

<sup>b</sup>Includes low serum haemoglobin level; elevated corrected serum calcium level; elevated serum lactate dehydrogenase level; poor performance status; and interval of <1 year between diagnosis and sunitinib treatment (Motzer *et al*, 2002).

<sup>c</sup>Mantel-Haenszel  $\chi^2$  test for general association.

<sup>d</sup>Risk factor included in the MSKCC prognostic model (Motzer *et al*, 2002).

<sup>e</sup>Fisher's exact test for general association when sample size requirement of the  $\chi^2$  test is not met.

Table 6. Final multivariate analysis of baseline characteristics predictive for long-term OS (i.e., OS  $\geq$  30 months) with sunitinib

Variable	Long-term OS				
	Median, months <sup>a</sup>	95% CI	HR	95% CI <sup>b</sup>	P-value <sup>c</sup>
<b>Ethnic origin</b>					
White	50.2	47.8–NR	0.339	0.131–0.877	0.0257
Non-white	38.4	35.7–NR			
<b>Bone metastases</b>					
Yes	42.7	37.5–NR	2.337	1.275–4.285	0.0061
No	54.5	47.8–NR			
<b>Baseline-corrected Ca<sup>d</sup></b>					
> 10 mg dl <sup>-1</sup>	41.7	33.6–41.7	4.356	1.658–11.44	0.0028
$\leq$ 10 mg dl <sup>-1</sup>	50.2	47.8–NR			
<b>Prior cytokine</b>					
Yes	47.9	39.8–NR	1.831	0.994–3.371	0.0522
No	NR	45.3–NR			

Abbreviation: Ca = calcium.

<sup>a</sup>On the basis of the Brookmeyer and Crowley method.

<sup>b</sup>On the basis of the Cox proportional-hazards model.

<sup>c</sup>Wald  $\chi^2$  test.

<sup>d</sup>Risk factor included in the MSKCC prognostic model (Motzer *et al*, 2002).

(HR, 0.764;  $P = 0.0096$ ), the pretreatment factors maintained their significance for predicting shorter survival, independent of treatment. For example, as comparison, the HRs for the MSKCC risk features were: anaemia (1.984), low performance status (1.942), time from diagnosis to treatment of <1 year (1.742), high-corrected calcium (2.146), and elevated lactate dehydrogenase (2.000). Tumour biology, reflected by these features, continues to drive OS, independent of the effect of sunitinib. As such, a better understanding of RCC biology is a priority. A tumour-specific biomarker(s) could enhance or replace prognostic models based on clinical features.

Like the analysis reported here, presence of bone metastasis was associated with shorter survival in an analysis with everolimus (Motzer *et al*, 2010). In that study, the population comprised patients who progressed on sunitinib and/or sorafenib. Clinically, patients treated with targeted agents may often first show signs of progression in bone metastases (Plimack *et al*, 2009). This could be a consequence of reduced vascularity in bone, as these agents are anti-angiogenesis drugs or some other aetiology. Studies that integrate radiation or other tumour-ablative techniques could be useful in treating RCC bone metastases. One multi-targeted TKI, cabozantinib, has achieved remarkable responses in bone metastases for prostate cancer (Hussain *et al*, 2011) and one phase Ib trial suggests a high level of activity in RCC (Choueiri *et al*, 2012). Studies with cabozantinib in metastatic RCC patients with bone metastases would be of high interest.

There were no significant differences in survival in white vs Asian patients. However, there was a trend for longer PFS in white patients compared with Asian patients, and white patients had a significantly longer PFS and OS compared with non-white, non-Asian patients. The latter finding could be linked to socioeconomic differences, which influenced outcome. These findings may also be accounted for by differences in baseline characteristics. However, given the extent of incomplete data, these differences and their potential impact on outcome require further investigation. Another

**Table 7.** Any grade treatment-emergent AEs occurring in 20% or more of patients in at least one ethnic subgroup

AE (any grade)	% of patients			P-value <sup>a</sup>	
	White (n = 884)	Asian (n = 70)	Non-white, non-Asian (n = 65)	White vs Asian	White vs non-white, non-Asian
Diarrhoea	64	54	66	0.1231	0.7894
Fatigue	64	53	58	0.0719	0.4233
Nausea	55	40	45	0.0173	0.0949
Dysgeusia	41	26	40	0.0154	1.0000
Vomiting	37	26	32	0.0538	0.5059
Decreased appetite	36	17	28	0.0015	0.2261
Dyspepsia	33	24	18	0.1832	0.0184
Hypertension	32	29	25	0.6886	0.2690
Stomatitis	30	20	14	0.1005	0.0064
Hand-foot syndrome	28	70	17	<0.0001	0.0610
Rash	27	24	23	0.6757	0.5630
Mucosal inflammation	26	40	18	0.0164	0.2366
Constipation	26	34	18	0.1600	0.1878
Arthralgia	24	11	14	0.0176	0.0911
Cough	23	26	17	0.6587	0.2862
Pain in extremity	23	14	26	0.1019	0.5446
Back pain	22	14	25	0.1718	0.6425
Dyspnoea	22	16	17	0.2304	0.3542
Epistaxis	21	20	12	0.8800	0.0831
Headache	21	19	15	0.6511	0.3420
Oedema peripheral	20	7	22	0.0067	0.7508
Dry skin	20	6	11	0.0022	0.0999
Anaemia	19	16	20	0.6326	0.7441
Skin discolouration	17	40	8	<0.0001	0.0553
Thrombocytopenia	17	19	22	0.7438	0.3970
Weight decreased	15	13	23	0.7297	0.1151
Anorexia	6	39	9	<0.0001	0.4328
Face oedema	4	20	NR	<0.0001	—

Abbreviation: NR = not reported (or <5% incidence).  
<sup>a</sup>P-value based on Fisher's exact test.

possible explanation for efficacy differences were differing rates of prior nephrectomy, an independent predictor of survival in both Asian and non-Asian patients (Naito *et al*, 2010; Patil *et al*, 2011). In the trials included in our analysis, the incidence of nephrectomy was much lower in Asian (24%) and non-white, non-Asian (68%) patients, compared with white patients (83%).

Differences in ethnic-based treatment tolerability may have also had a role. For example, *ad hoc* analyses indicated that several AEs occurred significantly more often in Asian patients, relative to white patients, such as hand-foot syndrome that occurred in 70% of Asian patients compared with 28% of white patients ( $P < 0.001$ ).

This is consistent with previous studies of sunitinib and sorafenib in Asian RCC patients, including Japanese, Chinese, and Korean patients (Sun *et al*, 2008; Hong *et al*, 2009; Lee *et al*, 2009; Tomita *et al*, 2010; Naito *et al*, 2011). For example, the incidences of hand-foot syndrome and hypertension were higher in Japanese and Chinese patients receiving sorafenib, in comparison with Western patients; similarly, thrombocytopenia and neutropenia occurred more frequently in Japanese and Korean patients receiving sunitinib. Such differences in tolerability in our study may have led to disparities in drug exposure due to higher discontinuation and/or dose reduction rates, which, in turn, may have diminished clinical benefit. On the other hand, several differences favoured Asian over white patients, and differences were less prominent between white and non-white, non-Asian patients, thus confounding a simple interpretation based on AEs only. Inter-ethnic pharmacokinetic and pharmacogenomic differences may explain the variation in tolerability and are under study (Kim *et al*, 2011).

Although this large database of 1059 patients enrolled to six clinical trials over 6 years provides a robust data set to analyse, study limitations are recognised. In addition to the usual issues associated with a retrospective analysis, the following may have confounded or led to difficulty in interpreting the results: data were missing for a significant proportion of patients in some categories of baseline information and subpopulations (e.g., risk factor data were missing for 40% of Asian patients); differences in sunitinib treatment schedules were not investigated for prognostic influence; there were imbalances in the numbers of patients in each ethnic subgroup and in some baseline characteristics; patients in clinical trials may represent a selective population; and, given the changes in the RCC treatment landscape during and after conduct of these trials, survival estimates may not be accurate representations of potential clinical benefit.

In conclusion, this analysis identified risk factors to survival with sunitinib and validated risk factors previously reported in advanced RCC. Potential ethnic-based differences in survival with sunitinib were identified. These factors may be applied to clinical trial design (e.g., patient eligibility and stratification) and interpretation of survival.

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## CONFLICT OF INTEREST

RJ Motzer reported receiving consultancy fees from Pfizer and research funding from Pfizer, GlaxoSmithKline, Novartis, AVEO Pharmaceuticals, and Bristol-Myers Squibb. B Escudier reported receiving honoraria from Pfizer. R Bukowski reported receiving consultancy fees, honoraria, and legal fees from Pfizer. BI Rini reported receiving consultancy fees and research funding from Pfizer. TE Hutson reported receiving research funding, consultancy fees, and honoraria from Pfizer, GlaxoSmithKline, AVEO Pharmaceuticals, and Novartis. CH Barrios reported receiving research funding, consultancy fees, and honoraria from Pfizer, GlaxoSmithKline, and Novartis. ME Gore reported receiving advisory board fees and honoraria from Pfizer. X Lin, K Fly and E Matczak are full-time employees of Pfizer and hold Pfizer stock.

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