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 (>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-naive patients with metastatic RCC (Motzer et al., 2009). In a randomised phase III trial, sunitinib demonstrated superior efficacy to interferon (IFN)-α 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 ≥ 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 ≥ 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 ≥ 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, NCT00779747, 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 ≥ 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 χ² test were included in the multivariate analysis. Further elimination was applied within the multivariate analysis to identify variables significant at P < 0.05.

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 χ² test (with Fisher’s exact test used when sample size requirements for the χ² 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 non-white, non-Asian, and 13% were non-white, non-Asian. A total of 83 patients (8%) had experienced a prior nephrectomy within one year of diagnosis.

**Table 1. Baseline patient characteristics**

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

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

*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).

*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) | 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                         |
| **ECOG PS, %**                 |                 |              |                              |                |                             |
| 0 (favourable)                 | 60              | 59           | 71                           | 0.819          | 0.096                       |
| 1 (intermediate)               | 38              | 40           | 28                           |                |                             |
| 2 (poor)                      | 2               | 1            | 2                            |                |                             |
| **Risk factors based on published MSKCC data, %** |  | | | | |
| 0 (favourable)                 | 44              | 10           | 35                           | <0.001         | 0.233                       |
| 1–2 (intermediate)             | 40              | 47           | 45                           |                |                             |
| >3 (poor)                     | 4               | 3            | 9                            |                |                             |
| Missing                       | 12              | 40           | 11                           |                |                             |
| **Histology, %**               |                 |              |                              |                |                             |
| Clear cell                    | 93              | 7            | 85                           | 0.079          | 0.046                       |
| Other                         | 7               | 9            | 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 (%)         | 83              | 24           | 68                           | <0.001         | 0.05                        |
| Prior cytokine use, %         | 25              | 23           | 14                           | 0.671          | 0.037                       |
| **Sites of metastasis, %**    |                 |              |                              |                |                             |
| 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

*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).

**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).

### Prognostic factors for PFS and OS with sunitinib

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 was 9.7 months (95% CI, 8.4–10.5 months) and 23.4 months (95% CI, 21.2–25.4 months), respectively (Figure 1).

![Figure 1. Kaplan–Meier curves of (A) PFS and (B) OS in all patients.](image-url)

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,
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; \( P = 0.0319 \)).

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

| Variable                  | PFS          | OS           |
|---------------------------|--------------|--------------|
|                           | Median, months\(^a\) | 95% CI  | HR      | 95% CI | P-value\(^b\) | Median, months\(^a\) | 95% CI | HR      | 95% CI | P-value\(^b\) |
| Ethnic origin             |              |              |         |        |              |              |         |        |        |              |         |        |
| 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      |         |        |              |              |         |        |        |              |         |        |
| ECOG PS\(^c\)            |              |              |         |        |              |              |         |        |        |              |         |        |
| \( \geq 1 \)              | 7.4          | 6.4–8.4      | 1.250   | 1.043–1.498 | 0.0159 | 14.1         | 10.0–11.7 | 1.302   | 13.0–16.3 | 0.0022 |
| 0                         | 10.7         | 10.0–11.7    |         |        |              |              |         |        |        |              |         |        |
| Time from diagnosis to treatment\(^c\) |          |              |         |        |              |              |         |        |        |              |         |        |
| \( \geq 1 \) year         | 11.8         | 10.6–13.7    | 0.814   | 0.680–0.975 | 0.0252 | 31.0         | 16.7      | 27.8–35.5 | 14.8–19.5 | 0.666  |
| \( < 1 \) year            | 7.4          | 6.4–8.1      |         |        |              |              |         |        |        |              |         |        |
| Bone metastases           |              |              |         |        |              |              |         |        |        |              |         |        |
| Yes                       | —            | —            | —       | —       | NS          | 16.1        | 27.8    | 14.0–18.2 | 24.4–30.9 | 1.535  |
| No                        | —            | —            | —       | —       | —           | 14.1        | 27.8    | 12.5–16.2 | 28.2–34.2 | 1.548  |
| Baseline Hgb\(^b\)        |              |              |         |        |              |              |         |        |        |              |         |        |
| \( \leq \) LLN             | 6.5          | 5.1–7.8      | 1.384   | 1.144–1.675 | 0.0008 | 13.7         | 10.7–12.6 | 13.7    | 12.5–16.2 | 0.0001 |
| > LLN                     | 11.1         | 10.7–12.6    |         |        |              |              |         |        |        |              |         |        |
| Baseline LDH\(^b\)        |              |              |         |        |              |              |         |        |        |              |         |        |
| > 1.5 \( \times \) ULN     | 4.1          | 2.8–6.9      | 1.664   | 1.201–2.305 | 0.0022 | 10.0         | 25.0      | 5.1–15.3 | 23.0–28.0 | 0.0123 |
| \( \leq 1.5 \times \) ULN  | 10.5         | 9.5–10.8     |         |        |              |              |         |        |        |              |         |        |
| Baseline-corrected Ca\(^b\) |              |              |         |        |              |              |         |        |        |              |         |        |
| > 10 mg dl\(^-1\)         | 5.1          | 4.0–7.6      | 1.374   | 1.080–1.747 | 0.0096 | 10.9         | 26.9      | 9.6–14.0 | 24.4–30.1 | 0.0001 |
| \( \leq 10 \) mg dl\(^-1\) | 10.6         | 9.7–10.9     |         |        |              |              |         |        |        |              |         |        |
| Baseline neutrophils      |              |              |         |        |              |              |         |        |        |              |         |        |
| \( \leq \) ULN             | 10.6         | 9.6–10.9     | 0.629   | 0.483–0.821 | 0.0006 | 25.1         | 11.7      | 23.0–28.2 | 6.6–13.7 | 0.017  |
| > ULN                     | 3.4          | 2.7–6.4      |         |        |              |              |         |        |        |              |         |        |
| Baseline platelets        |              |              |         |        |              |              |         |        |        |              |         |        |
| \( \leq \) ULN             | 10.7         | 10.0–11.3    | 0.607   | 0.469–0.785 | 0.0001 | 26.8         | 26.8      | 24.4–30.0 | 8.0–13.1 | 0.0055 |
| > ULN                     | 4.1          | 3.3–5.4      |         |        |              |              |         |        |        |              |         |        |
| Prior cytokine            |              |              |         |        |              |              |         |        |        |              |         |        |
| Yes                       | 8.3          | 7.8–9.7      | 1.342   | 1.085–1.659 | 0.0066 | 19.1         | 24.4      | 15.8–24.0 | 22.3–27.8 | 0.0068 |
| No                        | 10.0         | 9.0–10.7     |         |        |              |              |         |        |        |              |         |        |

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.

\(^a\)On the basis of Brookmeyer and Crowley method.

\(^b\)Wald \( \chi^2 \) test.

\(^c\)Risk factor included in the MSKCC prognostic model (Motzer et al, 2002).

Prognostic factors for long-term OS with sunitinib. Overall, 215 patients (20%) survived ≥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, 2.33; 95% CI, 1.27–4.28; 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%), dysguesia (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...
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Table 5. Baseline characteristics of patients with long-term OS (i.e., OS ≥ 30 months)

| Characteristic               | Long-term OS (n = 215) | Non-long-term OS (n = 844) | P-value |
|------------------------------|------------------------|---------------------------|---------|
| **Ethnic origin,** %         |                        |                           |         |
| White                        | 94                     | 81                        | 0.00002 |
| Non-white                    | 6                      | 15                        |         |
| Missing                      | 0                      | 5                         |         |
| **Risk factors based on published MSKCC data,** % b | | | |
| 0 (favourable)               | 70                     | 31                        | <0.0001 |
| 1–2 (intermediate)           | 28                     | 42                        |         |
| ≥ 3 (poor)                   | 0                      | 5                         |         |
| Missing                      | 1                      | 21                        |         |
| **ECOG PS,** %d | | | |
| 0                            | 75                     | 58                        | <0.0001 |
| 1                            | 25                     | 40                        |         |
| 2                            | 0                      | 3                         |         |
| **Prior nephrectomy,** %     |                        |                           |         |
| Yes                          | 96                     | 74                        | <0.0001 |
| No                           | 4                      | 19                        |         |
| Missing                      | 0                      | 7                         |         |
| **Prior cytokine,** %        |                        |                           |         |
| Yes                          | 21                     | 29                        | 0.0170  |
| No                           | 79                     | 71                        |         |
| Missing                      | 0                      | <1                        |         |
| **Baseline Hgb,** %d         |                        |                           |         |
| < LLN                        | 22                     | 44                        | <0.0001 |
| > LLN                        | 78                     | 56                        |         |
| Missing                      | 0                      | <1                        |         |
| **Baseline LDH,** %d         |                        |                           |         |
| > 1.5 × ULN                  | 3                      | 7                         | 0.0078  |
| ≤ 1.5 × ULN                  | 96                     | 78                        |         |
| Missing                      | 1                      | 15                        |         |
| **Baseline-corrected Ca,** %d|                        |                           |         |
| > 10 mg dl⁻¹                 | 5                      | 19                        | <0.0001 |
| ≤ 10 mg dl⁻¹                 | 95                     | 80                        |         |
| Missing                      | 0                      | 1                         |         |
| **Baseline neutrophils,** %  |                        |                           |         |
| < ULN                        | 97                     | 78                        | <0.0001 |
| > ULN                        | 2                      | 12                        |         |
| Missing                      | 1                      | 10                        |         |
| **Baseline platelets,** %    |                        |                           |         |
| < ULN                        | 96                     | 80                        | <0.0001 |
| > ULN                        | 4                      | 19                        |         |
| Missing                      | 0                      | <1                        |         |

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

*Pearson χ² test for general association.

On the basis of the Brookmeyer and Crowley method.

On the basis of the Cox proportional-hazards model.

Wald χ² test.

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 factors were: anaemia (1.884), 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 (Pilmaick 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
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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