Efficacy and safety of sunitinib in elderly patients with metastatic renal cell carcinoma

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Background: We retrospectively analyzed sunitinib outcome as a function of age in metastatic renal cell carcinoma (mRCC) patients.

Methods: Data were pooled from 1059 patients in six trials. Kaplan–Meier estimates of progression-free survival (PFS) and overall survival (OS) were compared by log-rank test between patients aged <70 (n = 857; 81%) and ≥70 (n = 202; 19%) years.

Results: In first-line patients, median PFS was comparable in younger and older patients, 9.9 vs 11.0 months, respectively (HR, 0.89; 95% CI: 0.73–1.09; P = 0.2629), as was median OS, 23.6 vs 25.6 months (HR, 0.93; 95% CI: 0.74–1.18; P = 0.5442). Similarly, in cytokine-refractory patients, median PFS was 8.1 vs 8.4 months (HR, 0.79; 95% CI: 0.49–1.28; P = 0.3350), while median OS was 20.2 vs 15.8 months (HR, 1.14; 95% CI: 0.73–1.79; P = 0.5657). Some treatment-emergent adverse events were significantly less common in younger vs older patients, including fatigue (60% vs 69%), cough (20% vs 29%), peripheral edema (17% vs 27%), anemia (18% vs 25%), decreased appetite (13% vs 29%), and thrombocytopenia (16% vs 25%; all P<0.05). Hand–foot syndrome was more common in younger patients (32% vs 24%).

Conclusions: Advanced age should not be a deterrent to sunitinib therapy and elderly patients may achieve additional clinical benefit.

The incidence of renal cell carcinoma (RCC) peaks between ages 60 and 70 years (Jungberg et al, 2010). Patients with RCC ≥65 years account for ~50% of those diagnosed in the United States of America and almost 70% of those dying from this tumor (Altekruse et al, 2010). Several studies have suggested that increasing age is an adverse prognostic factor in RCC, with older age associated with higher tumor stage and grade (Denzinger et al, 2007; Verhoest et al, 2007; Karadzic et al, 2008; Jung et al, 2009), although others have found that age has little impact on presentation or survival (Doherty et al, 1999; Thompson et al, 2008; Scoll et al, 2009). In general, survival tends to be poorer in older cancer patients (Bouchardy et al, 2003; Petignat et al, 2004; Quaglia et al, 2009; Janssen-Heijnen et al, 2010), reflecting a complex picture of less frequent referral to cancer specialists (Tydesley et al, 2000; Delva et al, 2011); inadequate treatment (Mor et al, 1985; Earle et al, 2002; Easson et al, 2002; Bouchardy et al, 2003; Houterman et al, 2006; Vulto et al, 2006); and impact of comorbidities (Extermann, 2007), since older patients are at significant risk for multiple comorbidities (e.g., 35% of patients age 65 years or older who are eligible for both US Medicare and Medicaid have ≥4 comorbidities (Fox and Reichard, 2013)). In addition, aging trends will only exacerbate this issue. In the United States, for example, people age 65 years or older represented 13% of the population in 2007; however, by 2030, this age group is projected to represent 19% of the population (US Department of Health and Human Services, 2009).

Keywords: sunitinib; renal cell carcinoma; metastatic; age; retrospective analysis
Therefore, it is imperative that the elderly are thoroughly assessed for suitability for treatment (National Comprehensive Cancer Network (NCCN), 2011) and that new treatments are adequately evaluated in this major segment of the cancer population. To date, however, elderly patients have been substantially underrepresented in oncology clinical trials (Lewis et al, 2003; Yee et al, 2003; Talarico et al, 2004; Yonemori et al, 2010). Potential reasons include greater frequency of comorbidities (and associated polypharmacy), some degree of baseline end-organ dysfunction, which may lead to failure to meet eligibility criteria or higher potential for renal and hepatic impairment, and concerns about toxicity and poor compliance (Kornblith et al, 2002; Yee et al, 2003; Aapro et al, 2005; Townsley et al, 2005).

Several new treatments have been approved for advanced RCC, and characterizing the safety and efficacy of these treatments in elderly patients is an important goal. One such treatment is sunitinib malate (SUTENT; Pfizer, New York, NY, USA), an orally administered, multitargeted inhibitor of receptors for vascular endothelial growth factor, platelet-derived growth factor, and other tyrosine kinases. Efficacy and safety of sunitinib in the first-line and cytokine-refractory settings have been demonstrated in six key clinical trials, using two different schedules: the approved schedule of 50 mg per day for 4 weeks on treatment followed by 2 weeks off treatment (Schedule 4/2), and a continuous daily dosing (CDD) schedule of 37.5 mg per day (Motzer et al, 2006a, b, 2007, 2009, 2012; Escudier et al, 2009; Barrios et al, 2012). Here, we report findings of a retrospective analysis using a pooled database of patients from these six trials in which we compared the efficacy and safety of sunitinib in patients aged <70 or ≥70 years.

MATERIALS AND METHODS

Patients. Eligibility criteria included age ≥18 years, histologically confirmed metastatic RCC, presence of measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 (Therasse et al, 2000), no known brain metastases, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (or Karnofsky performance status of ≥70% in one trial (Motzer et al, 2012)), and adequate organ function.

Study design. This retrospective analysis investigated the efficacy and safety of sunitinib as a function of age using pooled data from 1059 patients who received sunitinib in either the first-line or cytokine-refractory metastatic RCC setting in six prospective multinational Pfizer-sponsored clinical trials (Motzer et al, 2006a, b, 2007, 2009, 2012; Escudier et al, 2009; Barrios et al, 2012). Data from 360 patients treated with interferon alpha (IFN-α) in the first-line setting in one of the trials, a randomized phase III study, were also analyzed (Motzer et al, 2007, 2009). Sunitinib was administered orally at a starting dose of 50 mg per day on Schedule 4/2 in repeated 6-week cycles (n = 690; 65%), or 37.5 mg per day on the CDD schedule (n = 369; 35%). IFN-α was administered by subcutaneous injection thrice weekly on nonconsecutive days at 3 MU per dose in the first week, 6 MU the second week, and 9 MU thereafter. Treatment continued until disease progression, lack of clinical benefit, unacceptable toxicity, or consent withdrawal.

Efficacy endpoints included progression-free survival (PFS) and overall survival (OS). Tumor response and progression were assessed by investigators using RECIST version 1.0 (Therasse et al, 2000), and schedules specified in each trial protocol (initially every 4–6 weeks, increasing to every 8–12 weeks after ~6 months). Adverse events (AEs) were recorded regularly and graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE), version 3.0 (version 2.0 in one trial (Motzer et al, 2006a)).

Studies were run in accordance with the International Conference on Harmonization Good Clinical Practice guidelines (or Declaration of Helsinki) and applicable local regulatory requirements and laws, and approved by the institutional review boards/independent ethics committees of each participating center (ClinicalTrials.gov: NCT00267748, NCT00137423, NCT00083889, NCT00779747, NCT0054886, NCT00338844).

Statistical methods. Median PFS and OS for direct comparison of sunitinib-treated patients aged <70 and ≥70 years (including by treatment setting) were estimated by Kaplan–Meier method and compared using log-rank test. This age cutoff was chosen to address the increasing age expectancy in the general population, thus defining a population more representative of the elderly, and was the same one used in a previously reported analysis of elderly sorafenib-treated patients with advanced RCC (Eisen et al, 2008). A comparison of treatment-naïve patients on sunitinib vs IFN-α was performed using log-rank test. All hazard ratios (HRs) were calculated by Cox proportional hazards model. Pearson χ² test was used to assess differences in AE incidence rates between age groups. Differences in incidence rates of common treatment-emergent AEs (incidence ≥10%) were also assessed separately for patients in first-line trials only, and for patients who received sunitinib by the two different treatment schedules; P-values were calculated by two-sided Fisher’s exact test.

RESULTS

Baseline characteristics. Of 1059 sunitinib-treated patients, 857 (81%) were <70 years and 202 (19%) were ≥70 years (Table 1). The median age in the <70 and ≥70 years age groups was 57 years (range: 24–69) and 73 years (range: 70–87), respectively. Baseline characteristics of the two sunitinib age groups were generally similar, although more patients aged <70 years than ≥70 years were male (73% vs 59%) and had had a prior nephrectomy (81% vs 71%).

Baseline characteristics were also similar in the two age groups treated with IFN-α (Table 1). Of 360 patients, 299 (83%) were aged <70 with a median of 57 years (range: 38–69) and 61 (17%) were aged ≥70 years with a median of 74 years (range: 70–85).

Disposition and exposure in sunitinib-treated patients. Sunitinib treatment was administered to 783 first-line patients (74%) and 276 cytokine-refractory patients (26%). Across all trials, the overall proportion of patients remaining on treatment in the younger and older age groups was 12.3% and 8.9%, respectively. The most common reasons for discontinuing treatment included, in patients aged <70 vs ≥70 years, respectively, disease progression (20% vs 21%), death (1% vs 2%), AE (16% vs 27%), and consent withdrawal (2% vs 5%).

Exposure to sunitinib was comparable in younger and elderly age groups. Patients aged <70 and ≥70 years were treated for a median of 196 days (range: 2–1037) and 168 days (range: 3–840), respectively, and the median relative (percentage of actual/midpoint) dose intensity of sunitinib was 97.12% (range: 4.76–130.15%) and 89.72% (range: 7.14–270.24%), respectively. In patients aged <70 vs ≥70 years, 59% vs 68% had ≥1 dose interruption and 42% vs 57% had dose reductions.

Efficacy. Across the entire pooled sunitinib-treated population, PFS and OS were similar in younger and elderly sunitinib-treated patients. In the first-line treatment setting, for patients aged <70 and ≥70 years, respectively, median PFS was 9.9 vs 11.0 months with an HR of 0.89 (95% confidence interval (CI): 0.73–1.09; P = 0.2629), while median OS was 23.6 vs 25.6 months, with an HR of 0.93 (95% CI: 0.74–1.18; P = 0.5442). In the cytokine-refractory
treatment setting, for patients aged $<70$ and $\geq 70$ years, respectively, median PFS was 8.1 vs 8.4 months with an HR of 0.79 (95% CI: 0.49–1.28; $P = 0.3350$), while median OS was 20.2 vs 15.8 months, with an HR of 1.14 (95% CI: 0.73–1.79; $P = 0.5657$). Sunitinib efficacy was maintained in elderly patients, regardless of treatment setting (Table 2; Figure 1).

Within the first-line treatment setting, median PFS was significantly greater with sunitinib than with IFN-$\alpha$ in the groups of patients aged $<70$ and $\geq 70$ years ($P < 0.0197$), and median OS was also improved in each age group, although this difference did not reach significance (Table 3).

Safety in sunitinib-treated patients by age. The incidences of most treatment-emergent AEs were similar in both age groups (Table 4). Some events, however, were significantly more common ($P < 0.05$) in patients aged $\geq 70$ years compared with those aged $<70$ years.

### Table 1. Baseline patient characteristics

| Characteristic                              | Sunitinib | IFN-$\alpha$ |
|--------------------------------------------|-----------|--------------|
| Age $< 70$ years (n = 857)                 | Age $\geq 70$ years (n = 202) | Age $< 70$ years (n = 299) | Age $\geq 70$ years (n = 61) |
| Median (range) age, years                  | 57 (24–69) | 73 (70–87) | 57 (38–69) | 74 (70–85) |
| Male/female, %                            | 73/27     | 59/41       | 74/26      | 67/33      |
| ECOG PS, n (%)                            | 0         | 1           | 2          |            |
| 0 (favorable)                              | 533 (62)  | 114 (56)    | 185 (62)   | 34 (56)    |
| 1–2 (intermediate)                        | 309 (36)  | 81 (40)     | 113 (38)   | 24 (39)    |
| >3 (poor)                                  | 15 (2)    | 7 (3)       | 1 (<1)     | 3 (5)      |
| Missing                                    | 152 (18)  | 32 (16)     | 3 (1)      | 0          |
| Risk factors based on published MSKCC data, n (%)<sup>a</sup> | | | | |
| 0 (favorable)                              | 342 (40)  | 74 (37)     | 175 (59)   | 32 (53)    |
| 1–2 (intermediate)                        | 326 (38)  | 88 (44)     | 107 (36)   | 27 (44)    |
| >3 (poor)                                  | 37 (4)    | 8 (4)       | 14 (5)     | 2 (3)      |
| Missing                                    | 152 (18)  | 32 (16)     | 3 (1)      | 0          |
| Histology, n (%)<sup>b</sup>              |          |             |            |            |
| Clear cell                                 | 833 (97)  | 194 (96)    | 289 (97)   | 61 (100)   |
| Other                                      | 22 (3)    | 7 (4)       | 10 (3)     | 0          |
| Mean (range) time since initial diagnosis, years | 2.4 (0–28.3) | 3.1 (0–24.6) | 2.1 (0–20.6) | 4.2 (0.1–21.3) |
| Prior nephrectomy, n (%)<sup>b</sup>      | 690 (81)  | 143 (71)    | 267 (89)   | 55 (90)    |
| Sites of metastasis, n (%)                 |          |             |            |            |
| Lung                                      | 657 (77)  | 163 (81)    | 236 (79)   | 48 (79)    |
| Liver                                     | 196 (23)  | 50 (25)     | 72 (24)    | 15 (25)    |
| Bone                                      | 261 (31)  | 50 (25)     | 87 (29)    | 20 (33)    |

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

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

<sup>b</sup> Histology data missing for three patients (<1%); nephrectomy data missing for 57 patients (4%).

### Table 2. Progression-free and overall survival by treatment setting and age in sunitinib-treated patients

| Median time to event (95% CI), months | Age $<70$ years | Age $\geq70$ years | Hazard ratio (95% CI) | P-value<sup>a</sup> |
|--------------------------------------|-----------------|--------------------|----------------------|--------------------|
| First-line mRCC treatment           |                 |                    |                      |                    |
| Progression-free survival            | 9.9 (8.3–10.7)  | 11.0 (9.0–14.8)    | 0.89 (0.73–1.09)     | 0.2629             |
| Overall survival                     | 23.6 (21.2–27.6)| 25.6 (21.7–38.4)   | 0.93 (0.74–1.18)     | 0.5442             |
| Cytokine-refractory mRCC treatment  |                 |                    |                      |                    |
| Progression-free survival            | 8.1 (7.8–8.7)   | 8.4 (6.3–14.3)     | 0.79 (0.49–1.28)     | 0.3350             |
| Overall survival                     | 20.2 (16.2–25.1)| 15.8 (13.7–24.0)   | 1.14 (0.73–1.79)     | 0.5657             |

Abbreviations: CI = confidence interval; mRCC = metastatic renal cell carcinoma.

<sup>a</sup> Log-rank test.
<70 years (Table 4), including fatigue, cough, anemia, peripheral edema, thrombocytopenia, decreased weight, decreased appetite, dizziness, hypothyroidism, dehydration, and urinary tract infection. Hand–foot syndrome, hair color changes, and chest pain were all more common in younger patients. A similar profile of age-associated differences in the incidence of common treatment-emergent AEs (i.e., events reported in ≥10%) was observed when the analysis was limited to patients in first-line treatment trials only (data not shown). Although, overall, the incidence profile of common treatment-emergent AEs was broadly similar to that observed in the total patient population, there were a few differences. In patients who received sunitinib on Schedule 4/2, the incidences of fatigue, dizziness, dehydration, and hand–foot syndrome were not significantly different between the two age groups; constipation, asthenia, anorexia, and erythema were significantly more common in older patients, and pyrexia and flatulence were significantly more common in younger patients. Among patients who received sunitinib on CDD, the incidences of anemia and hand–foot syndrome were not significantly different between the two age groups.

Table 3. Comparison of PFS and OS in the first-line treatment setting by treatment and age

| Event          | Statistic                        | Sunitinib Age <70 years | IFN-α Age <70 years | Sunitinib Age ≥70 years | IFN-α Age ≥70 years |
|----------------|----------------------------------|-------------------------|---------------------|-------------------------|---------------------|
| PFS Median     | time to event (95% CI), months   | 9.9 (8.3–10.7)          | 5.0 (3.8–5.3)       | 11.0 (9.0–14.7)         | 7.9 (3.9–10.8)      |
| Hazard ratio   | (95% CI)                         | 0.58 (0.50–0.69)        |                     | 0.62 (0.41–0.93)        |                     |
| P-value        |                                 | 0.0000                  |                     | 0.0197                  |                     |
| OS Median      | time to event (95% CI), months   | 23.5 (21.1–27.6)        | 22.7 (17.9–27.5)    | 25.5 (21.6–38.4)        | 17.5 (13.7–31.1)    |
| Hazard ratio   | (95% CI)                         | 0.99 (0.82–1.19)        |                     | 0.71 (0.49–1.02)        |                     |
| P-value        |                                 | 0.8781                  |                     | 0.0623                  |                     |

Abbreviations: CI = confidence interval; IFN-α = interferon alpha; OS = overall survival; PFS = progression-free survival.

Figure 1. Kaplan–Meier estimates of survival in sunitinib-treated patients by age (<70 vs ≥70 years). (A) Progression-free survival in the first-line setting; (B) overall survival in the first-line setting; (C) progression-free survival in the cytokine-refractory setting; (D) overall survival in the cytokine-refractory setting.
Sunitinib age analyses in metastatic RCC

Table 4. Common treatment-emergent adverse events occurring in sunitinib-treated patients <70 vs ≥70 years of age

| Adverse event                  | Age < 70 years (n = 857) | Age ≥ 70 years (n = 202) | P-valueb |
|--------------------------------|--------------------------|--------------------------|----------|
| Diarrhea                       | 551 (64)                 | 128 (63)                 | 0.8072   |
| Fatigue                        | 510 (60)                 | 139 (69)                 | 0.0159   |
| Nausea                         | 455 (53)                 | 115 (57)                 | 0.3469   |
| Dysgeusia                      | 341 (40)                 | 74 (37)                  | 0.4240   |
| Vomiting                       | 316 (37)                 | 71 (35)                  | 0.6850   |
| Hypertension                   | 273 (32)                 | 73 (36)                  | 0.2442   |
| Dyspepsia                      | 280 (33)                 | 57 (28)                  | 0.2402   |
| Hand-foot syndrome             | 275 (32)                 | 48 (24)                  | 0.0218   |
| Stomatitis                     | 248 (29)                 | 67 (33)                  | 0.2660   |
| Anorexia                       | 234 (27)                 | 62 (31)                  | 0.3387   |
| Rash                           | 226 (26)                 | 57 (28)                  | 0.5967   |
| Constipation                   | 215 (25)                 | 61 (30)                  | 0.1538   |
| Mucosal inflammation           | 213 (25)                 | 60 (30)                  | 0.1796   |
| Pain in extremity              | 208 (24)                 | 38 (18)                  | 0.1151   |
| Arthralgia                     | 186 (22)                 | 48 (24)                  | 0.5111   |
| Back pain                      | 190 (22)                 | 41 (20)                  | 0.6359   |
| Cough                          | 172 (20)                 | 59 (29)                  | 0.0059   |
| Dyspnea                        | 190 (22)                 | 39 (19)                  | 0.3942   |
| Epistaxis                      | 175 (20)                 | 45 (22)                  | 0.5636   |
| Headache                       | 184 (21)                 | 35 (17)                  | 0.2099   |
| Asthenia                       | 163 (19)                 | 50 (25)                  | 0.0787   |
| Anemia                         | 150 (18)                 | 51 (25)                  | 0.0163   |
| Peripheral edema               | 144 (17)                 | 54 (27)                  | 0.0018   |
| Hair color changes             | 175 (20)                 | 17 (8)                   | <0.0001  |
| Pyrexia                        | 162 (19)                 | 26 (13)                  | 0.0513   |
| Dry skin                       | 147 (17)                 | 40 (20)                  | 0.4117   |
| Skin discoloration             | 147 (17)                 | 38 (18)                  | 0.6066   |
| Thrombocytopenia               | 135 (16)                 | 50 (25)                  | 0.0038   |
| Weight decreased               | 134 (16)                 | 49 (24)                  | 0.0051   |
| Abdominal pain                 | 149 (17)                 | 28 (14)                  | 0.2498   |
| Appetite decreased             | 114 (13)                 | 58 (29)                  | <0.0001  |
| Neutropenia                    | 124 (14)                 | 40 (20)                  | 0.0661   |
| Insomnia                       | 124 (14)                 | 30 (15)                  | 0.9117   |
| Dizziness                      | 102 (12)                 | 38 (19)                  | 0.0111   |
| Myalgia                        | 100 (12)                 | 23 (11)                  | 1.0000   |
| Hypothyroidism                 | 88 (10)                  | 35 (17)                  | 0.0070   |
| Abdominal pain upper           | 101 (12)                 | 20 (10)                  | 0.5387   |
| Oral pain                      | 96 (11)                  | 24 (12)                  | 0.8052   |
| Dehydration                    | 82 (10)                  | 36 (18)                  | 0.0017   |
| Chills                         | 91 (11)                  | 26 (13)                  | 0.3823   |
| Chest pain                     | 102 (12)                 | 14 (7)                   | 0.0448   |
| Erythema                       | 85 (10)                  | 25 (12)                  | 0.3060   |
| Flatulence                     | 95 (11)                  | 13 (6)                   | 0.0524   |
| Alopecia                       | 81 (9)                   | 25 (12)                  | 0.2401   |
| Gastroesophageal reflux disease| 86 (10)                  | 14 (7)                   | 0.2277   |

*Graded as per National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, and occurring in ≥10% of patients, statistically significantly different incidences between age groups (P<0.05) shown in bold.

DISCUSSION

This retrospective, pooled analysis found that sunitinib efficacy was comparable in elderly (≥70 years) and younger (<70 years) patients with metastatic RCC, regardless of treatment setting. Elderly patients treated with IFN-α in a randomized phase III study vs sunitinib in the first-line setting (Motzer et al, 2007, 2009) also derived similar benefit as younger patients randomized to IFN-α; however, the survival benefits of sunitinib over IFN-α were not observed for IFN-α-resistant RCC patients. Nonetheless, our findings support observations from an expanded access trial of sunitinib with less restrictive eligibility criteria, in which PFS and OS for elderly patients (1418 patients; 32% of the population), although defined differently (≥65 years), were comparable with those of the overall population, median age 59 years (range: 19–89; Gore et al, 2009). Correspondingly, although the definition of ‘elderly’ can be arbitrary, our analyses suggest that, regardless of the age cutoff used, there is no apparent difference in outcome with sunitinib.
Table 5. Overall treatment-emergent adverse events by highest grade/severity in sunitinib-treated patients <70 vs ≥70 years of age

| Maximum CTCAE grade | Age <70 years (n = 857) | Age ≥70 years (n = 202) | P-value* |
|---------------------|-------------------------|-------------------------|----------|
| 1                   | 33 (4)                  | 2 (1)                   | <0.001   |
| 2                   | 170 (20)                | 18 (9)                  |          |
| 3                   | 452 (53)                | 137 (68)                |          |
| 4                   | 130 (15)                | 29 (14)                 |          |
| 5                   | 69 (8)                  | 15 (7)                  |          |
| Missing/Unknown     | 3 (<1)                  | 1 (<1)                  |          |

Abbreviation: CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.
*Mantel–Haenszel mean score test.

Although there was no significant difference in PFS or OS between age groups, there was a trend toward improved PFS in older sunitinib-treated patients in the overall population (i.e., both treatment settings combined) with median PFS of 10.9 months compared with 9.0 months in younger patients (HR, 0.85; 95% CI: 0.70–1.02; P = 0.0830). A similar trend was reported for elderly patients (≥70 years) receiving sorafenib (Eisen et al, 2008), raising the possibility that elderly patients with RCC may be more responsive to anti-angiogenic therapy; although, in our analysis, IFN-α-treated elderly patients also seemed to benefit more than younger ones from treatment (median PFS 7.9 vs 5.0 months). These studies, however, contradict a recently reported retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) registry in which disease-specific survival was inferior in older adults (≥75 years) with metastatic RCC (Nelson et al, 2013); also, in contrast to younger patients, older patients in the SEER analysis did not experience an improvement in survival in the ‘targeted therapy era’ (2005–2009) relative to the ‘cytokine era’ (1992–2004). Of note, however, this analysis did not report comorbidity data that may have confounded the results; only patients with de novo metastatic disease and thus inherently intermediate- or poor-risk disease were included. In addition, the registry lacked data pertaining to the systemic therapies received; thus, actual practice patterns could not be confirmed. Preclinical studies have shown that there are age-dependent differences in tumor growth, but these patterns are not consistent across tumor types (Pili et al, 1994; Anisimov, 2006; Reed et al, 2007). Also, a recent RCC tumor biopsy study revealed age-related differences in tumor vasculature, in which clear cell RCC tumors from patients aged ≥65 years had significantly higher microvascular density than those from patients aged <65 years, and markers of angiogenic activity also differed (Meehan et al, 2011). Further work is needed on a larger number of tumor samples, but it is conceivable that the higher microvascular density in older patients results in greater sensitivity to anti-angiogenic treatment or that higher vessel density is inversely associated with tumor aggressiveness (Yildiz et al, 2008).

Our analysis showed that the AE profile was broadly similar in older and younger patients for the total patient population, in first-line patients, and regardless of treatment schedule. Some AEs, such as fatigue, were significantly more common in older patients, and the profile of the highest grade AEs was overall significantly more severe in older patients (younger patients were more likely to have a highest grade AE of grade 1 or 2, and older patients more likely to have a highest grade AE of grade 3), possibly due to more comorbidities in this population. Similar observations were made in a recently reported retrospective analysis of elderly patients with metastatic RCC in which patients ≥75 years received fewer lines of systemic therapy as compared with other age-based subsets and more frequently discontinued therapies due to toxicity (Pal et al, 2013). However, importantly, the increased incidences of certain AEs in our analysis did not impact on overall efficacy in the elderly population, despite observed trends for increased dosing interruptions, reductions, and treatment discontinuations. Of note, hand–foot syndrome was more common in younger patients, possibly due to relatively higher activity levels, resulting in increased pressure on the hands and feet. While it is difficult to generalize across therapeutic agents, our study adds to a growing number of publications suggesting that older patients can tolerate molecularly targeted agents as well as younger patients (Pal et al, 2011). However, further post-marketing data for the elderly population are needed, in addition to results from clinical trials in which patients may not represent the general population, in order to fully assess response and tolerability in the presence of comorbidities. In addition, there may be potential pharmacokinetic differences in this population, which might explain our findings.

The results reported here demonstrate that the efficacy profile of sunitinib appears comparable in older and younger patients with advanced RCC, with some limited differences in the safety profiles. Therefore, advanced age alone should not be a deterrent to treating with sunitinib in this population, nor should less effective or non-recommended treatment options be chosen (National Comprehensive Cancer Network (NCCN), 2011) due to concerns regarding age-related tolerability; and, in fact, elderly patients may achieve additional clinical benefit with sunitinib.

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CONFLICT OF INTEREST

RMB received honoraria and consultant fees from Pfizer, Novartis, Genentech, GlaxoSmithKline, and Bristol-Myers Squibb, and consultant fees from Argos and Exelixis. BIR received research funding and consultant fees from Pfizer. MEG received advisory board and speaker bureau fees from Pfizer, Bayer, Roche, Novartis, GlaxoSmithKline, and Aveo/Astellas, and acknowledges NHS funding to the NIHR Biomedical Research Centre. JML received research funding, honoraria, and consultant fees from Pfizer, Novartis, Bristol-Myers Squibb, and GlaxoSmithKline, and acknowledges NHS funding to the NIHR Biomedical Research Centre. BE received advisory fees from Pfizer, GlaxoSmithKline, Novartis, Bayer, and Aveo; XL, KE, and EM are compensated employees of Pfizer and own Pfizer stock. BM is a former employee of Pfizer. RJM received research funding from Pfizer, GlaxoSmithKline, Novartis, and Bristol-Myers Squibb, and consultant fees from Pfizer and Genentech. The remaining authors declare no conflict of interest.

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