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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 $\geqslant 70$ ($n=202$; 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 (Ljungberg *et al*, 2010). Patients with RCC $\geqslant 65$ years account for $\sim 50\%$ 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; Karakiewicz *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 (Tyldesley *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 $\geqslant 4$ 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).

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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 $\geqslant 70$ years.

MATERIALS AND METHODS

Patients. Eligibility criteria included age $\geqslant 18$ 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 $\geqslant 70\%$ 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 $\sim$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, NCT00077974, NCT00054886, NCT00338884).

Statistical methods. Median PFS and OS for direct comparison of sunitinib-treated patients aged <70 and $\geqslant 70$ 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 χ^2 test was used to assess differences in AE incidence rates between age groups. Differences in incidence rates of common treatment-emergent AEs (incidence $\geqslant 10\%$) 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 $\geqslant 70$ years (Table 1). The median age in the <70 and $\geqslant 70$ 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 $\geqslant 70$ 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 $\geqslant 70$ 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* $\geqslant 70$ 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 $\geqslant 70$ 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/intended) 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* $\geqslant 70$ years, 59% *vs* 68% had $\geqslant 1$ 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 $\geqslant 70$ 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 ⩾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-α in the groups of patients aged <70 and ⩾70 years ($P\leqslant 0.0197$), 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 ⩾70 years compared with those aged

Table 1. Baseline patient characteristics

	Sunitinib		IFN-α	
Characteristic	**Age <70 years (*n*=857)**	**Age ⩾70 years (*n*=202)**	**Age <70 years (*n*=299)**	**Age ⩾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	533 (62)	114 (56)	185 (62)	34 (56)
1	309 (36)	81 (40)	113 (38)	24 (39)
2	15 (2)	7 (3)	1 (<1)	3 (5)
Risk factors based on published MSKCC data, *n* (%)[a]				
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* (%)[b]				
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* (%)[b]	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-α = interferon alpha; MSKCC = Memorial Sloan-Kettering Cancer Center.
[a]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).
[b]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 ⩾70 years**	**Hazard ratio (95% CI)**	***P*-value[a]**
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.
[a]Log-rank test.

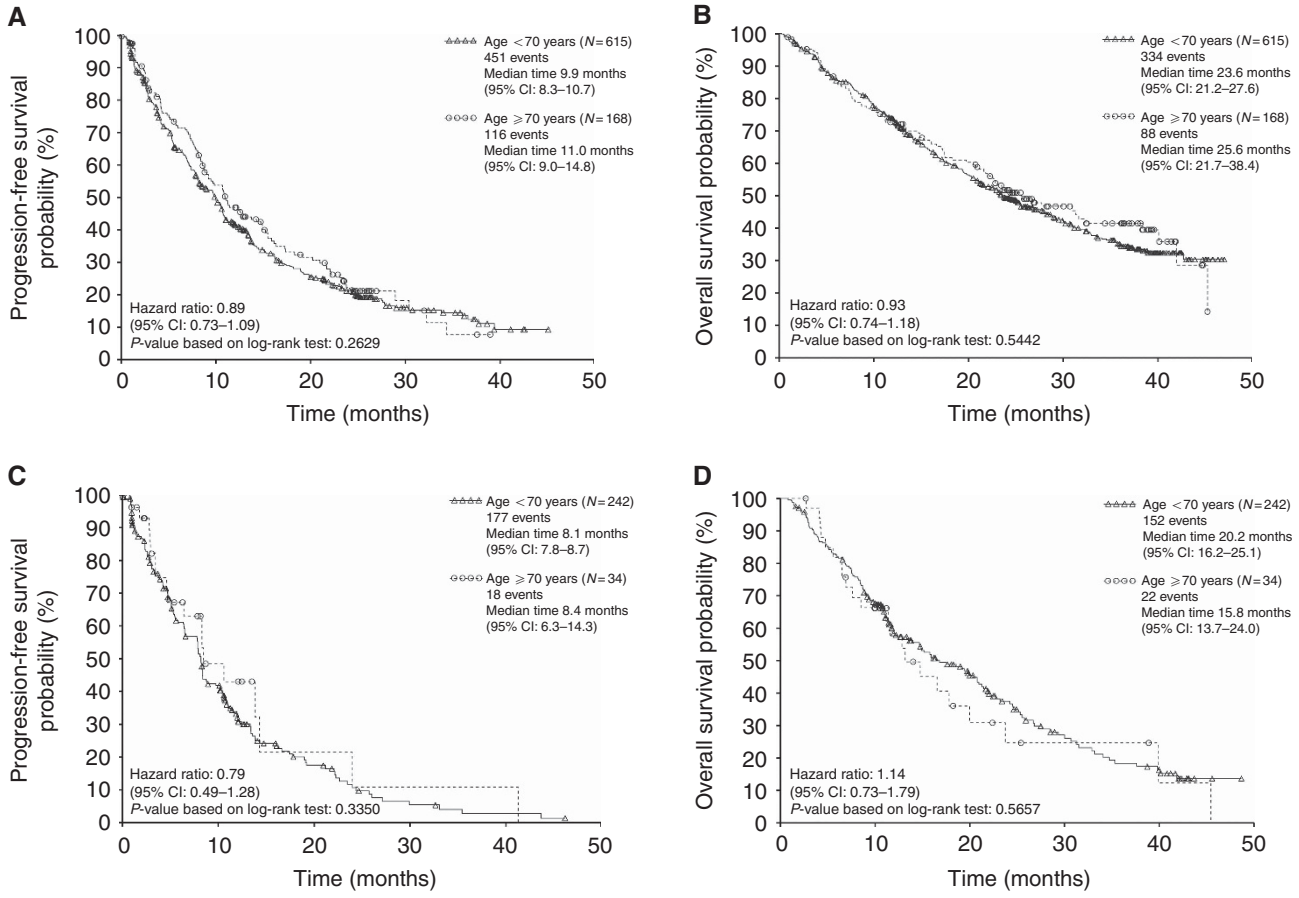

Figure 1. Kaplan–Meier estimates of survival in sunitinib-treated patients by age (<70 *vs* ⩾70 years). (**A**) Progression-free survival in the first-line setting; (**B**) overall survival in the first-line setting; (**C**) progression-free survival in the cytokine-refractory setting; (**D**) overall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

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

		Age <70 years		Age ⩾70 years	
Event	**Statistic**	**Sunitinib**	**IFN-α**	**Sunitinib**	**IFN-α**
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) *P*-value[a]	0.58 (0.50–0.69) 0.0000		0.62 (0.41–0.93) 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) *P*-value[a]	0.99 (0.82–1.19) 0.8781		0.71 (0.49–1.02) 0.0623	

Abbreviations: CI = confidence interval; IFN-α = interferon alpha; OS = overall survival; PFS = progression-free survival.
[a]χ^2-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).

Patients who received sunitinib by the two different treatment schedules (Schedule 4/2 and CDD) were analyzed separately (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 4. Common treatment-emergent adverse events occurring in sunitinib-treated patients <70 *vs* ⩾70 years of age[a]

	Number of patients (%)		
Adverse event	**Age <70 years (*n* = 857)**	**Age ⩾70 years (*n* = 202)**	***P*-value[b]**
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 (19)	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 (19)	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
Depression	73 (9)	21 (10)	0.4096
Dry mouth	72 (8)	22 (11)	0.2717
Urinary tract infection	**32 (4)**	**29 (14)**	**<0.0001**

[a]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.
[b]Pearson χ^2-test.

and nausea, hyponatremia, arthralgia, and pruritus were significantly more common in older patients.

Overall, treatment-emergent AEs by highest grade/severity were compared for the two age groups. The profiles were significantly different for patients aged <70 years and ⩾70 years, irrespective of whether data for all trials were considered together or if data from first-line and cytokine-refractory trials were considered separately ($P<0.001$, $P=0.023$, and $P=0.035$, respectively). Overall, treatment-emergent AEs by highest grade in each age group, for all trials (first-line and cytokine-refractory combined) are summarized in Table 5. These data show that a greater proportion of the younger patients had highest severity of grade 1 or 2 and the older patients were more likely to have a highest severity of grade 3. There was no difference in the occurrence of highest grade AEs of grade 4 or 5 between the two age groups, with the majority of grade 5 AEs occurring in treatment-naïve patients regardless of age (aged <70: $n=51$; aged ⩾70: $n=13$).

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 in this trial were maintained in both age groups. Our analysis is limited by its exploratory nature, and the fact that the study was not designed to test for statistically significant differences in efficacy or safety between patients aged <70 and ⩾70 years. Although baseline characteristics of older and younger sunitinib-treated patients appeared balanced (apart from gender), risk factor data were missing for 17%; any imbalance in these data may have influenced results. In addition, because these patients were treated in clinical trials, they may represent a more selective patient population that is not adequately reflective of a real-world setting in which elderly patients warrant special consideration given the risk of AEs with targeted therapy. 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

	Number of patients (%)		
Maximum CTCAE grade	**Age <70 years (*n* = 857)**	**Age ⩾70 years (*n* = 202)**	***P*-value[a]**
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.
[a]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, KF, 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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