Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial


Summary

Background Results from clinical trials have established sunitinib as a standard of care for first-line treatment of advanced or metastatic renal-cell carcinoma (RCC); however, many patients, particularly those with a poorer prognosis, do not meet inclusion criteria and little is known about the activity of sunitinib in these subgroups. The primary objective of this trial was to provide sunitinib on a compassionate-use basis to trial-eligible patients with RCC from countries where regulatory approval had not been granted.

Methods Previously treated and treatment-naive patients at least 18 years of age with metastatic RCC were eligible. All patients received open-label sunitinib 50 mg orally once daily on schedule 4-2 (4 weeks on treatment, 2 weeks off). Safety was assessed regularly, tumour measurements done per local practice, and survival data collected where possible. Analyses were done in the modified intention-to-treat (ITT) population, which consisted of all patients who received at least one dose of sunitinib. This study is registered with ClinicalTrials.gov, NCT00130897.

Findings As of December, 2007, 4564 patients were enrolled in 52 countries. 4371 patients were included in the modified ITT population. This population included 321 (7%) patients with brain metastases, 582 (13%) with Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher, 588 (13%) non-clear-cell RCC, and 1418 (32%) aged 65 years or more. Patients received a median of five treatment cycles (range 1–25). Reasons for discontinuation included lack of efficacy (n=1168 [27%]) and adverse events (n=362 [8%]). The most common treatment-related adverse events were diarrhoea (n=1936 [44%]) and fatigue (n=1606 [37%]). The most common grade 3–4 adverse events were fatigue (n=344 [8%]) and thrombocytopenia (n=338 [8%]) with incidences of grade 3–4 adverse events similar across subgroups. In 3464 evaluable patients, the objective response rate (ORR) was 17% (n=603), with subgroup ORR as follows: brain metastases (26 of 213 [12%]), ECOG performance status 2 or higher (29 of 319 [9%]), non-clear-cell RCC (48 of 437 [11%]) and age 65 years or more (176 of 1056 [17%]). Median progression-free survival was 10.9 months (95% CI 10.3–11.2) and overall survival was 18.4 months (17.4–19.2).

Interpretation In a broad population of patients with metastatic RCC, the safety profile of sunitinib 50 mg once-daily (initial dose) on schedule 4-2 was manageable and efficacy results were encouraging, particularly in subgroups associated with poor prognosis who are not usually entered into clinical trials.

Funding Pfizer Inc.

Introduction Kidney cancer accounts for almost 3% of adult malignancies globally with more than 310,000 new cases and 100,000 deaths annually.1 5-year survival for patients diagnosed with early-stage renal cell carcinoma (RCC) is as high as 66%.2 However, for the 30% of patients with RCC who present with advanced or metastatic disease, 5-year survival is only 10%.3,4 Additionally, local recurrence or distant metastasis develops in up to 40% of patients treated for localised tumours.4,5

Sunitinib malate (Pfizer Inc; New York, NY, USA) is an oral, multitargeted receptor tyrosine kinase (RTK) inhibitor of vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and other RTKs with direct antitumour and antiangiogenic activity.6,7 It has been approved worldwide for the first-line and second-line treatment of advanced RCC.

Sunitinib showed impressive activity in two sequential single-arm phase II trials of patients with cytokine-refractory metastatic RCC.8,9 In a multicentre, randomised phase III trial of 750 treatment-naive patients with metastatic RCC, sunitinib showed significantly better efficacy than interferon α.10 By investigator assessment, the objective response rate (ORR) was 37% versus 9%, respectively (p<0.001), and median progression-free survival (PFS) was 11 versus 4 months, respectively (p=0.001). This trial established sunitinib as a reference standard of care for first-line treatment of metastatic RCC. A recent update of this trial reported a median overall survival of more than 2 years (26–4 months) for patients given sunitinib, compared with 21.8 months for those given interferon α (hazard ratio=0.821, 95% CI 0.673–1.001; p=0.0510).20 A commonly asked question is whether patients with RCC in clinical trials are representative of the general population for this disease. Many patients with RCC do not meet inclusion criteria, particularly those with a poorer prognosis. For instance, 10–20% of patients with metastatic RCC are treated for localised tumours.4,6 In the sunitinib therapy trial, 58% of patients enrolled had metastatic disease at presentation.4,6

As of December, 2007, 4564 patients were enrolled in 52 countries. 4371 patients were included in the modified ITT population, which consisted of all patients who received at least one dose of sunitinib. This study is registered with ClinicalTrials.gov, NCT00130897.
RCC present with brain metastases, these patients can have an extremely short life expectancy, 4–6 months, and are poorly represented in trials. Similarly, patients with metastatic RCC and a poor performance status have a shorter survival and are often excluded from clinical trials. Additionally, RCC trials tend to focus on patients with clear-cell histology, the predominant histological subtype, and exclude patients with other histologies. Thus, little is known about the activity of targeted therapies, such as sunitinib, in these subsets of patients.

We report results of sunitinib use derived from an ongoing, global, expanded-access study of patients with metastatic RCC, the aim of which was to provide sunitinib on a compassionate-use basis to patients in countries where regulatory approval had not yet been granted, and who did not otherwise have access to sunitinib because of trial ineligibility.

**Methods**

**Patients**

This expanded-access study is ongoing at 246 sites in 52 countries (in North, Central, and Latin America, Europe, Asia-Pacific, Australia, and Africa). The first patient was enrolled in June, 2005. Accrual has discontinued on a country-by-country basis according to treatment availability. The last patient enrolled in December, 2007.

Inclusion criteria were: age 18 years or more; histologically confirmed metastatic RCC (of all histological subtypes); adequate organ function; resolution of all acute toxic effects of prior systemic therapy; radiotherapy or surgical procedure to grade 1 or less per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0; ineligibility (determined at screening) for participation in ongoing sunitinib studies open to enrolment at the institution; and the potential to derive clinical benefit from sunitinib treatment as judged by the investigator. Adequate organ function was defined by the following criteria: total serum bilirubin less than or equal to twice the upper normal limit (ULN; patients with Gilbert’s disease exempt); serum aminotransferases less than five-times ULN; serum creatinine less than or equal to twice ULN; absolute neutrophil count of 1000 per μL or more without growth factor support; platelets 75 000 per μL or more; and haemoglobin 80 g/L or more. Both previously treated and treatment-naïve patients were eligible, the latter by a protocol amendment in February, 2006. Before this amendment, we planned to enrol around 1007 patients; after the amendment, we planned to enrol around 5000.

Patients who previously received sunitinib were excluded, as were patients with any acute medical or psychiatric condition that, in the investigator’s judgment, would make inclusion inappropriate.

This study was approved by the institutional review board (IRB) or independent ethics committee (IEC) at each participating centre and done in accordance with the International Conference on Harmonization Good Clinical Practice guidelines. Patients gave written informed consent.

**Procedures**

Sunitinib was provided by Pfizer Inc and self-administered at a 50 mg starting dose orally once-daily, without regard to meals, in repeated 6-week cycles of 4 weeks on treatment, followed by 2 weeks off (schedule 4-2). Dose reductions to 37·5 mg/day and then to 25 mg/day were permitted on the basis of individual tolerability. Patients received sunitinib until disease progression, unacceptable toxicity, or withdrawal of consent. Palliative radiotherapy

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
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<tbody>
<tr>
<td>Sex (male)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
</tr>
<tr>
<td>ECOG PS</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
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<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
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<td>Histology</td>
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<td>Clear cell</td>
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<tr>
<td>Other</td>
</tr>
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<td>Prior nephrectomy</td>
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<tr>
<td>Number of metastatic sites</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>≥2</td>
</tr>
<tr>
<td>Site of metastasis</td>
</tr>
<tr>
<td>Lungs</td>
</tr>
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<td>Lymph nodes</td>
</tr>
<tr>
<td>Bone</td>
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<td>Liver</td>
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<td>Brain</td>
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<tr>
<td>Prior therapy</td>
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<tr>
<td>Antiangiogenic</td>
</tr>
<tr>
<td>Cytokines</td>
</tr>
<tr>
<td>Modified MSKCC risk group</td>
</tr>
<tr>
<td>Favourable</td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
<tr>
<td>Poor</td>
</tr>
<tr>
<td>Missing</td>
</tr>
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</table>

Data are n (%). Median age was 59·0 years (range 19·0–89·0). Missing data: sex (n=9), ECOG PS (n=94), histology (n=25); prior nephrectomy status (n=203); prior cytokine therapy (n=16). ECOG PS=Eastern Cooperative Oncology Group performance status; MSKCC=Memorial Sloan-Kettering Cancer Center. *Risk factors are ECOG PS ≥2, low haemoglobin, and high calcium. For patients without prior cytokine treatment, additional risk factors were raised lactate dehydrogenase and time-to-use of interferon α of <1 year. Patients with prior cytokine treatment were categorized as favourable, intermediate or poor if 0, 1, or >1 risk factors were present, respectively. Patients with prior cytokine treatment were categorized as favourable, intermediate or poor if 0, 1-2, or >2 risk factors were present, respectively.

Table 1: Baseline patient characteristics in all 4371 patients (modified intention-to-treat population)
to specific sites of disease was permitted (except to target lesions), per the protocol, if considered medically necessary by the treating physician. In such cases, sunitinib was interrupted during palliative radiotherapy, stopping one day before and resuming treatment one day after.

Disease assessment and a physical examination were done at screening, at which time safety and tolerability (using NCI CTCAE version 3.0), concomitant medication use, biochemistry, and haematology were also assessed.

The primary objective was to provide sunitinib to patients who did not have access to the drug, but who had the potential of deriving clinical benefit. Secondary objectives included assessment of toxicity and efficacy and to examine these parameters in subgroups with a poor prognosis.

Collection of safety data was mandated and specified in the protocol. Toxicity was assessed on days 1, 14, and 28 of cycle 1, and on days 1 and 28 of subsequent cycles. Adverse events were graded according to NCI CTCAE, version 3.0. The association between adverse events and sunitinib therapy was assessed by the investigator. Patients who discontinued therapy because of an adverse event continued follow-up until symptoms resolved or stabilised.

No specific schedule or type of tumour measurements or assessments were mandated in the protocol. Instead, tumour assessments were done per local standard pattern of care for RCC, and data on response, PFS, and overall survival were collected where possible. ORR was defined as the number of complete and partial responses according to Response Evaluation Criteria in Solid Tumours (RECIST). PFS was defined as the time from start of therapy to disease progression or death due to any cause. Overall survival was defined as the time from start of therapy to death due to any cause (with survival times censored at last follow-up for patients remaining alive).

Statistical analysis
Consistent with the nature of expanded-access trials, sample size was not predetermined, no inferential analyses were planned, and no hypotheses were to be tested. Safety and efficacy data were analysed for all patients who received at least one dose of study drug—a modified intention-to-treat (ITT) population. ORR was calculated with the corresponding 95% two-sided CI, using standard methods based on binomial distribution. Estimates of median PFS and overall survival were derived using the Kaplan-Meier method, and 95% CI were calculated with standard methods for a fixed-sample, single-stage design. All statistical analysis was done using SAS version 9.1.1.

This study is registered with ClinicalTrials.gov, NCT00130897.

Role of the funding source
This trial was designed by Pfizer, the sponsor, in collaboration with the investigators and MEG, the principal investigator. All logistical aspects of this trial were managed by Pfizer. Data were collected and analysed by Pfizer in collaboration with the corresponding author and the other authors. The corresponding author had full access to all data and vouches for the accuracy and completeness of the data presentation and analysis. The decision to publish this analysis and final decisions with regard to the content of the manuscript were made by the corresponding author in consultation with the other authors.

Results
As of December, 2007, 4564 patients had been enrolled and patients are no longer being recruited. At the time of analysis, data for safety, treatment duration, tumour response, and survival were available for 4371 patients, comprising the modified ITT population. Most patients had prior nephrectomy, and only a few had prior antiangiogenic therapy (table 1). Most patients had an ECOG performance status of 0–1 and clear-cell histology. The main site of metastasis was lung (table 1). More than

<table>
<thead>
<tr>
<th>Non-haematological</th>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
<th>Grade 5* (death)</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Diarrhoea</td>
<td>1734 (40)</td>
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<td>32 (1)</td>
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<tr>
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<td>10 (&lt;1)</td>
<td>0</td>
<td>11 (&lt;1)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Haematological</th>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
<th>Grade 5* (death)</th>
<th>Total</th>
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<tr>
<td>Thrombocytopenia</td>
<td>610 (14)</td>
<td>338 (8)</td>
<td>1 (&lt;1)</td>
<td>949 (22)</td>
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<tr>
<td>Anaemia</td>
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<td>155 (4)</td>
<td>0</td>
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<td>Neutropenia</td>
<td>396 (9)</td>
<td>266 (6)</td>
<td>0</td>
<td>662 (15)</td>
</tr>
</tbody>
</table>

Data are number of patients (%). *A total of 63 patients (1%) died from treatment-related adverse events (data not shown).

Table 2: Treatment-related adverse events of interest and those that occurred in at least 10% of all 4371 patients (modified intention-to-treat population)
two-thirds of patients had prior systemic cytokine therapy (table 1). Baseline characteristics were similar for those with or without prior cytokine treatment, with one exception; a higher proportion of patients with prior cytokine treatment (335 of 2974 [11%]) were classified as poor risk on MSKCC criteria than were those without (40 of 1381 [3%]).

The median number of treatment cycles was five (range 1–25) with a median follow-up duration of 11·6 months (<1–28·0). The mean relative dose intensity was 95·2% (SD 25·3). Treatment duration was similar in patients with or without prior cytokine therapy. However, median duration of follow-up was longer in those who had previously received cytokine therapy than for those who had not, at 12·7 months (range <1–28·0) compared with 9·8 months (<1–25·0), respectively.

Sunitinib doses were reduced from 50 mg/day to 37·5 mg/day in 1446 of 4371 patients (33%) with further reductions to 25 mg/day in 586 patients (13%) and, although not permitted per protocol, to 12·5 mg/day in 18 patients (<1%). All patients began treatment on schedule 4-2 but could be placed on a daily continuous dosing schedule, upon dose reduction, at the investigator’s discretion. There were fewer dose reductions in patients without prior cytokine therapy (598 of 1381 [43%]) than for those with prior therapy (1446 of 2974 [49%]).

Reasons for discontinuation included lack of efficacy (1168 of 4371 [27%]), adverse events (362 of 4371 [8%]), and withdrawal of consent (253 of 4371 [6%]), all of which occurred slightly less frequently in patients without prior cytokine therapy than in those with prior therapy (data not shown).

The most commonly reported treatment-related non-haematological adverse events were diarrhoea, fatigue, nausea, and mucosal inflammation, most of which were of grade 1–2 severity (table 1). The most common grade 3–4 treatment-related non-haematological adverse events were fatigue, hand-foot syndrome, asthenia, hypertension, and diarrhoea (table 1). The most common grade 3–4 haematological treatment-related adverse events included thrombocytopenia and neutropenia (table 1). 63 (1%) patients died from treatment-related adverse events, including one from fatigue, one from asthenia, three of cardiac failure, and one from thrombocytopenia. The most common treatment-related deaths were renal failure (n=5), hepatic failure (n=4), and cardiac failure, gastrointestinal haemorrhage, sepsis, and pulmonary embolism (all n=3).
The incidences of the most commonly reported grade 3–4 treatment-related adverse events for all patients did not differ markedly from those with brain metastases, poor performance status, non-clear-cell RCC, or elderly individuals (data not shown). For example, the overall incidence of grade 3–4 treatment-related adverse events in patients with brain metastases was comparable to the incidence in the overall population, with the most commonly reported grade 3–4 adverse events of fatigue and asthenia occurring in 7% of patients (23 of 321 and 21 of 321, respectively) and thrombocytopenia in 6% (19 of 321). The overall incidence of any-grade treatment-related adverse events was also comparable in this subgroup of patients (296 of 321; 92%) to that of the general population of patients with RCC (4020 of 4371; 92%), in which the most commonly reported events were diarrhoea (110 of 321; 34%) and fatigue (103 of 321; 32%). Additionally, only one patient with brain metastases experienced a cerebral haemorrhage that was considered to be treatment-related; this haemorrhage was mild in severity (grade 1–2).

Treatment-related hypothyroidism was reported in 261 of 4371 patients (6%), most of whom reported symptoms of grade 1–2 severity; routine testing of thyroid function was not required. The total incidence of grade 3 or worse treatment-related cardiac disorders was 1% (55 of 4371) with less than 1% of patients (12 of 4371) experiencing cardiac failure. 522 of 4371 patients (12%) died on study (or within 28 days of their last dose) and 1379 of 4371 patients (32%) died during follow-up. 346 patients were evaluable for tumour response; 34 of 3464 patients (1%) had a complete response and 569 of 3464 patients (16%) a partial response, yielding an ORR of 17% (603 of 4371; 92%). The ORR was similar regardless of prior cytokine treatment status (table 3). ORR for elderly patients was comparable to that of the overall population (table 3). Responses were also seen in patients with brain metastases, non-clear-cell histology, and poor performance status (table 3).

59% of patients (2029 of 3464) exhibited stable disease for at least 3 months, irrespective of prior cytokine treatment status, resulting in a clinical benefit rate (ORR plus stable disease ≥3 months) of 76% (2632 of 3464; table 3). Patients who were elderly and had non-clear-cell histology had comparable rates of stable disease to that of the overall population, whereas rates of stable disease were somewhat lower in patients with poor performance status and brain metastases. Median PFS was 10·9 months (95% CI 10·3–11·2) for the overall population (figure A; table 4) with negligible differences between patients with or without prior cytokine therapy. Median PFS for elderly patients was comparable to that of the overall population; however, PFS was reduced in the other subgroups (table 4). Median PFS by MSKCC risk group was: 14·6 months (95% CI 13·8–15·6) in the favourable risk group (n=1585), 8·5 months (8·1–9·2) in the intermediate risk group (n=1928), and 4·1 months (3·1–5·0) in the poor risk group (n=373). Baseline MSKCC data were missing for 472 patients.

Median overall survival was 18·4 months (17·4–19·2) in the overall population (figure B, table 4) with similar overall survival in patients with and without prior cytokine therapy. Median overall survival for elderly patients was also comparable to that of the overall population, but overall survival was reduced in the other subgroups (table 4). Median overall survival by MSKCC risk group was: 24·7 months (23·5–NA) in the favourable risk group (n=1585), 14·4 months (95% CI 13·8–15·6) in the intermediate risk group (n=1928), and 5·3 months (4·6–6·4) in the poor risk group (n=373).

### Discussion

We have shown the safety of sunitinib in a broad RCC population, particularly in subgroups who might be predicted to tolerate therapy less well than patients in well-defined, selected populations in the initial phase II and III trials. Furthermore, we have shown that the safety profile of sunitinib is very similar for these poor-prognosis groups to that reported in well-defined patient populations. This assertion is supported by the observation that the overall incidence of dose modifications and discontinuations in this report is very similar to those seen within the pivotal phase II and III trials, and that the overall incidence of adverse events in this study is slightly less than in these trials.

Correspondingly, it might seem that there was a discrepancy between the relatively low incidence of grade 3–4 adverse events in this trial and the apparently high percentage of dose reductions. However, this observation might be due to the fact that, although patients...
began treatment on schedule 4-2, they could be placed on a
daily continuous dosing schedule at the investigator's
discretion. Otherwise, guidelines for dose reduction on the
basis of individual tolerability were specified in the
protocol, and hypotheses regarding any apparent
discrepancies may be premature for this ongoing trial.

We recently reported a preliminary analysis of our
safety data comparing toxicity in patients who had been
exposed to sunitinib for less than 6 months with those
who received therapy for longer.22 The results were as
expected; patients treated for a longer duration
experienced a comparative increase in the overall
incidence of treatment-related adverse events. However,
no new or unexpected toxicities occurred23 and, import-antly, there was no apparent increase in grade 3 or
higher cardiac toxicities associated with more prolonged
therapy. We recognise that, because of the nature of
expanded-access reports, some omissions in adverse event
reporting may occur, despite the use of mandated and
standardised assessment criteria and monitoring, as in
this study.

Within the analysis reported here, the total incidence of
grade 3 or higher treatment-related cardiac disorders was
only 1% (55 of 4371) with less than 1% of patients (12 of
4371) experiencing cardiac failure. These data are similar
to those included in the approved labelling for sunitinib,24
which states that left ventricular dysfunction was reported
in three of 375 patients (1%) and congestive heart failure
in one of 375 patients (<1%) who received sunitinib as
first-line therapy for metastatic RCC in a randomised,
phase III trial of sunitinib versus interferon α. Nonethe-
less, routine monitoring is recommended for
patients with cardiac risk factors and baseline evaluation
of ejection fraction is recommended for consideration in
patients with baseline ejection fraction values of <50%.
This may explain why the ORR reported
here is lower than that in other studies of single-agent
sunitinib. Additionally, a dose-response relationship has
been established for sunitinib25 and one-third of our
patients (1446 of 4371) had a dose reduction. The PFS and
overall survival data are very consistent with previous
reports and show improvement on historical data for the
subgroups reported here; for example, median overall
survival times in this trial were 9.2, 6.7, and 13.4 months
compared with historical data of 4.0–6.0, 4.8, and
9.4 months for patients with brain metastases,26 poor
performance status,27 and non-clear cell histology,28
respectively. Moreover, in our four subgroups, there is
evidence of activity. These results, combined with the
tolerability data, should encourage prospective studies of
sunitinib, and possibly other therapies, in patients
otherwise considered unsuitable because of tolerability
concerns. Indeed, our data suggest that toxicity should
not preclude prospective trials in these patients.

Anecdotal reports have suggested that sunitinib has
activity against brain metastases.27–29 This activity is not
unexpected; animal studies have shown that sunitinib or
its active metabolite penetrates the central nervous
system.30 In this trial, brain-specific tumour response
measures were not used. Additionally, no data are
available regarding the number of patients who had prior
irradiation of brain metastases or who received palliative
radiotherapy while on the study. Thus, further
investigation is warranted. Nonetheless, the safety profile
of patients with brain metastases was comparable to that
of the overall population in this trial. These findings
support a previous report of preliminary data from this
subgroup,22 in which the rates of sunitinib dose reduc-
tions and discontinuations were similar to that of the
overall population (as were baseline patient
characteristics). However, at the data cut-off for the
present analysis, the median number of treatment cycles
received by patients with brain metastases (three, range
1–25) was somewhat less than that of the overall
population, as was the mean relative dose intensity of
92.7% (SD 20.24), and so the safety profile for this
subgroup also requires further investigation.

The observation that efficacy was not apparently
affected by prior cytokine treatment might be important,
because some patients may derive benefit from cytokine
therapy and then gain further benefit from subsequent
sequential treatment with a targeted agent. The data
presented here suggests that such a strategy would, at the
least, not be detrimental, although this hypothesis needs
to be tested in a prospective, randomised trial.

Despite the encouraging findings from this trial, some
aspects of its design were not ideal and somewhat limited
the value of the data, specifically with regard to the
efficacy results. For example, because tumour assessment
was performed according to local standard of care, data
were available for 3464 patients (out of 4371 patients in
the modified intention-to-treat population) who were
evaluable for tumour response (ie, data were missing for
21% of patients). Also, because this was not a randomised,
controlled trial, survival benefit cannot be weighed
properly since it must be compared against historical
controls.

In summary, this study highlights the benefits that can
be accrued from expanded-access programmes by
allowing collection and exploratory analyses of the safety
profile and efficacy data in groups of patients that might
otherwise be excluded from prospective clinical trials. In
particular, we have shown that sunitinib is safe and
toxicity manageable in subgroups of patients that might
otherwise have lower tolerance to therapy. Efficacy
appears to be consistent with the benefits shown in
prospective RCC studies. These results should encourage the study of targeted agents in subgroups of patients otherwise excluded from trials and, therefore, potentially disadvantaged.

Contributors
The final manuscript was written by MEG with substantive input from all authors and with logistical and editorial assistance, which was funded by Pfizer Inc, provided by ACUMED of Tytherington, UK (medical writer Andy Gannon).

Conflicts of interest
MEG has received speaker bureau and advisory board fees from Pfizer. CS received advisory fees from Pfizer. CP has received speaker and advisory fees from Pfizer, Bayer Schering, Roche, Wyeth, and Novartis. SB has received consultant or advisory fees from Bayer, Pfizer, Roche, Wyeth, and Novartis and honoraria from Novartis. GAB has received honoraria from Pfizer. SO has received honoraria from Bayer, Pfizer, and Wyeth. S-HL has received honoraria and consultant or advisory fees from Pfizer. PS has received honoraria, travel grants, and unrestricted research grants from Pfizer. RB has received honoraria from Pfizer, Genentech, Novartis, Wyeth, and Bayer, and consultant fees from Pfizer, Genentech, Novartis, GlaxoSmithKline, Wyeth, and Bayer, and has provided expert testimony for Novartis. SH, AN, and JY are full-time employees of Pfizer. JH, DC, EV, and PM reported no potential conflicts of interest.

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