EUROPEAN JOURNAL OF CANCER 46 (2010) 2432–2440

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Long-term safety of sorafenib in advanced renal cell carcinoma: Follow-up of patients from phase III TARGET

Thomas E. Hutson [a,], Joaquim Bellmunt [b], Camillo Porta [c], Cezary Szczylik [d], Michael Staehler [e], Andrea Nadel [f], Sibyl Anderson [g], Ronald Bukowski [h], Tim Eisen [i], Bernard Escudier [j,**], For the Sorafenib TARGET Clinical Trial Group*

[a] *Texas Oncology at Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA*
[b] *University Hospital del Mar and Vall d'Hebron University Hospital, Barcelona, Spain*
[c] *I.R.C.C.S. San Matteo University Hospital Foundation, Pavia, Italy*
[d] *Military School of Medicine, Warsaw, Poland*
[e] *Universitätsklinikum Großhadern, Munich, Germany*
[f] *Bayer Healthcare Pharmaceuticals Inc., Montville, NJ, USA*
[g] *Bayer Healthcare Pharmaceuticals Inc., Wayne, NJ, USA*
[h] *Cleveland Clinic Taussig Cancer Center, Cleveland, OH, USA*
[i] *Cambridge Biomedical Research Centre, Cambridge, UK*
[j] *Institut Gustave Roussy, Villejuif, France*

ARTICLE INFO

Article history:
Received 30 March 2010
Received in revised form 21 June 2010
Accepted 21 June 2010
Available online 23 July 2010

Keywords:
Renal cell carcinoma
Long-term safety
Sorafenib
Tolerability
TARGET
Disease stabilisation

ABSTRACT

Background: The phase III Treatment Approaches in Renal cancer Global Evaluation Trial (TARGET) indicated that sorafenib is effective and well tolerated in advanced renal cell carcinoma patients. However, few data have been published on the safety of long-term sorafenib treatment. A retrospective subgroup analysis was performed to evaluate the efficacy and safety of sorafenib in patients in TARGET who received treatment for >1 year.

Methods: The present subgroup analysis (based on the September 2006 database with updated safety analysis) evaluated the efficacy and safety of sorafenib in all patients in the sorafenib arm of TARGET who were treated for >1 year. The assessments included the overall survival, progression-free survival (PFS), disease control rate (DCR), and safety. The patients remained on therapy post-progression at the discretion of the investigator.

Results: In TARGET, 169 patients received treatment with sorafenib for >1 year. The median PFS of patients in this subpopulation was 10.9 months from the date of randomisation, with a DCR of 92%. The most commonly reported treatment-related adverse events of any grade were diarrhoea (74%), rash/desquamation (51%), hand–foot skin reaction (49%), alopecia (39%), and fatigue (38%). Adverse events were mild to moderate, and presented early in the course of the treatment; there were no unexpected toxicities associated with the long-term administration of sorafenib.

Conclusions: Results of this subgroup analysis of patients enrolled in TARGET who received treatment for >1 year indicate that long-term treatment with sorafenib is associated with continued efficacy and a well-tolerated safety profile.

* *Corresponding author:* Address: Texas Oncology, PA, Baylor Sammons Cancer Center, 3535 Worth Street, Collins Building, Dallas, TX 75246, USA. Tel.: +1 214 370 1945; fax: +1 214 370 1902.
** *Corresponding author*: Address: Institut Gustave Roussy, 39 Rue Camille Desmoulins, Desmoulins, Villejuif, Paris F-94805, France. Tel.: +33 (0)1 42114476; fax: +33 (0)1 42115211.
E-mail addresses: thomas.hutson@usoncology.com (T.E. Hutson), escudier@igr.fr (B. Escudier).
0959-8049/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.ejca.2010.06.121

1. Introduction

Development of multi-targeted tyrosine kinase inhibitors (TKIs) was the first therapeutic breakthrough in advanced renal cell carcinoma (RCC) since the demonstration in 2001 of longer survival with the use of interferon-α after cytoreductive nephrectomy.[1,2] TKIs interfere with the pathways controlling angiogenesis and cell proliferation in advanced RCC; clear-cell RCC, the most common histologic subtype, is marked by high levels of proangiogenic growth factors generated by inactivation of the Von Hippel–Lindau (*VHL*) gene.[3] In 2005, sorafenib became the first TKI to be approved for the treatment of advanced RCC by the US Food and Drug Administration (FDA). Other drugs with a similar therapeutic strategy include sunitinib (approved by the FDA in 2006) and pazopanib (approved by the FDA in 2009). TKIs are effective treatments, with mild to moderate toxicity; they have achieved objective response rates ranging from 5% to 45%.[4–10] However, the relatively short time of these drugs in the market precluded a thorough evaluation of the tolerability of long-term administration. To date, no retrospective or prospective studies have been published reporting on the safety of long-term treatment with a targeted therapy in RCC.

The efficacy and tolerability of sorafenib were demonstrated in the phase III randomised, double-blind, placebo-controlled Treatment Approaches in Renal cancer Global Evaluation Trial (TARGET). Sorafenib is an orally active multikinase inhibitor that blocks vascular endothelial growth factor receptor (VEGFR)-2 and -3, platelet-derived growth factor receptor (PDGFR)-β, Flt-3, c-KIT, and the intracellular serine/threonine kinase RAF-1.[5,11,12] In clinical practice and in the trial setting, sorafenib was effective and well tolerated in at-risk populations, including patients with renal impairment and elderly patients, for whom treatment-associated adverse events (AEs) may present a greater burden.[13–15]

In TARGET, results of a preplanned interim analysis (conducted in January 2005) indicated that sorafenib doubled progression-free survival (PFS) compared with the placebo (5.5 versus 2.8 months, respectively; HR, 0.44; 95% CI, 0.35–0.55; $P < 0.0001$).[5] In May 2005, patients randomised to placebo were permitted to cross over to the sorafenib arm of the study. In the final overall survival (OS) analysis conducted 16 months post-crossover (September 2006), median survival in the sorafenib group was longer than in the placebo group, but these results did not reach significance because of a confounding effect of crossover (17.8 versus 15.2 months, respectively; HR, 0.78; $P = 0.146$).[12] The results of a secondary OS analysis that censored the placebo patients at crossover revealed a significant survival advantage with sorafenib (17.8 versus 14.3 months; HR, 0.78; $P = 0.029$).[12] Sorafenib was well tolerated across patients in TARGET, the most common AEs being diarrhoea, hand–foot skin reaction (HFSR), fatigue, and rash.

Because the trial took place before the approval of sorafenib and other TKIs, TARGET investigators were given the option of continuing patients on sorafenib for extended courses of therapy if the patients did not experience disease progression or if the patients experienced clinical benefit despite the growth of the primary lesion. Based on the data collected from these patients, we conducted a retrospective study to explore the safety and efficacy of long-term (>1 year) sorafenib administration.

2. Patients and methods

2.1. Study design

This report describes a retrospective analysis of patients in TARGET who received sorafenib for >1 year. The study design and patient inclusion criteria have been previously described.[5] Briefly, TARGET was a phase III, double-blind, multinational, randomised, parallel-group, multicentre trial in patients with unresectable and/or metastatic RCC who had undergone 1 prior systemic therapy. Other eligibility criteria included age ⩾18 years, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–2, favourable- or intermediate-risk Memorial Sloan-Kettering Cancer Center (MSKCC) score, and adequate bone marrow, liver, pancreas, and kidney function.

Patients were stratified by country and MSKCC prognostic score prior to randomisation to sorafenib 400 mg bid or placebo groups in a 1:1 ratio with a block size of 4. The treatment was administered in 6-week cycles for the first 24 weeks and 8-week cycles thereafter on a continuous schedule. Treatment interruptions and up to 2 dose reductions (first to 400 mg/d, then 400 mg every 2 d) were permitted for the treatment-related toxicities. The treatment continued until disease progression or withdrawal from the study because of intolerable toxicities.

Patients receiving sorafenib could continue open-label treatment beyond radiologic progression at the discretion of the investigator if disease progressed in some locations but improved in others; progressive disease (PD) occurred at one site but stable disease (SD) was achieved at other sites; and/or PD occurred but radiologic changes suggestive of response were detected (e.g., cavitary changes, decreased pleural effusion). The patients could also continue sorafenib beyond PD if their clinical symptoms improved.

2.2. Outcome variables

The original primary end-point of TARGET was OS, measured from the date of enrollment to death. The secondary end-points included PFS (defined as the time from random assignment to disease progression based on the imaging or clinical assessment using Response Evaluation Criteria In Solid Tumors [RECIST]). The tertiary end-points included disease control rate (DCR; defined as the proportion of patients who achieved confirmed complete response [CR], partial response [PR], or SD on the basis of RECIST, which was maintained for ⩾28 d following the first demonstration of response), time to response, and patient-reported outcomes. Safety was evaluated every 3 weeks during the first 24 weeks of treatment, and every 4 weeks thereafter. AEs were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. A toxicity assessment was conducted 30 d after the discontinuation of the study drug. After treatment conclusion, the patients were contacted every 3 months to determine the survival status until death or loss to follow-up was documented.

2.3. Statistical analysis

The subgroup analysis was conducted for the intent-to-treat population in patients who received sorafenib for >1 year, as determined by the comparisons of the first and last date of treatment. This analysis was performed on the final updated OS analysis (September 2006),[12] with updated safety analysis for those patients who continued on study and had not been transferred to a commercial supply or the Sorafenib Long-term Extension Program (STEP). Eighty-four patients in the sorafenib arm and 67 patients who crossed over to sorafenib were still on therapy at cutoff. Six patients who crossed over to sorafenib received sorafenib for >1 year, but were not included in this analysis because of the concern that the disease progression that may have occurred while receiving placebo would not permit inclusion into the subpopulation described in this manuscript.

Statistical analyses performed were exploratory, and results are mostly descriptive in nature. Descriptive statistics were used to describe patient characteristics, best tumour response, and safety in patients who received sorafenib for >1 year. Kaplan–Meier estimates and curves were used to summarise time-to-event data, including PFS. Treatment-emergent AEs, serious AEs (SAEs), and AEs leading to discontinuation and/or withdrawal from the study are summarised. To present safety data over a continuous time frame, crossover treatment cycles were appended to be labelled sequentially with the double-blind treatment cycles, ignoring any possible gaps in the treatment between the 2 phases.

3. Results

3.1. Patients

One hundred and sixty-nine patients randomised to the sorafenib arm of TARGET received sorafenib for >1 year; these patients were a subpopulation of the 451 patients randomised to receive sorafenib in TARGET ($n = 903$). The baseline characteristics of patients in the long-term treatment subpopulation and patients in the overall sorafenib arm, which has been previously described,[5] are shown in Table 1. The median age in the long-term treatment subpopulation was 60 years (range, 19–80 years), the majority of the patients were male (71%), and most patients had ECOG PS 0 or 1 (57% and 42%, respectively) and/or favourable MSKCC score (67%). Most patients had undergone nephrectomy and/or cytokine-based chemotherapy (96% and 83%, respectively). The most common sites of baseline metastases were lung (74%), liver (23%), and bone (18%). Underlying cardiovascular disease was common, with 46% of patients having hypertension and 13% having coronary artery or ischaemic heart disease.

3.2. Exposure to sorafenib

The median duration of therapy for the long-term treatment subpopulation was 18.9 months (range, 12.1–30.2 months); 27 patients remained on sorafenib for >2 years. The reasons for discontinuation are presented in Supplementary Table 1. The median dose of sorafenib was 797 mg/d (range, 232.7–1067.8 mg/d) (Supplementary Table 2). Forty-five percent of the patients ($n = 76$) did not require dose reduction or interruption during therapy.

3.3. Efficacy

The median OS had not been reached by September 2006 for the 169 patients who received sorafenib treatment for >1 year, although the 18-month and 24-month survival rates were 88% and 69%, respectively. The median PFS was 10.9 months (95% CI, 9.3, 12.8) from the date of randomisation (Fig. 1). One hundred and thirty-one patients received sorafenib post-progression; 35 patients in this subpopulation did not experience disease progression during their enrolment in TARGET. Two patients experienced CR and 36 experienced PR, generating an overall response rate (ORR; CR + PR) of 23% (95% CI, 16.4, 29.5). One hundred and twenty-six patients (74.6%; 95% CI, 67.3, 80.9) achieved SD (Table 2). Three percent (95% CI, 1.0, 6.8) had PD as their best response. The DCR was 92% (95% CI, 87.2, 95.8). Among the 38 patients who achieved a CR or PR, the median time to response was 2.8 months (range, 1.3–15.3 months).

3.4. Safety

Most patients (160 of 169 patients; 95%) experienced $\geqslant 1$ treatment-related AE of any grade during their enrolment in TARGET. AEs were primarily grade 1 or 2; grade 3/4 AEs occurred in 34% of patients (Table 3). The most common AEs of any grade were diarrhoea (74%), rash/desquamation (51%), HFSR (49%), alopecia (39%), fatigue (38%), and hypertension (25%). HFSR and hypertension were the most common grade 3/4 AEs (7% and 5%, respectively). The rates of treatment-related cardiac ischaemia/infarction (2%) or left ventricular systolic dysfunction (1%) were low. Treatment-related cardiovascular or bleeding SAEs included 2 incidents (1%) each of hypertension and cardiac ischaemia/infarction and single incidents (1%) each of colon haemorrhage, bronchopulmonary haemorrhage, thrombosis/thrombus/embolism, and anaemia. Nineteen patients (11%) experienced drug-related SAEs.

3.5. Sorafenib dose interruption or reduction

As noted, 45% of the patients ($n = 76$) did not require dose reduction or interruption during sorafenib therapy. For the other 55% of patients ($n = 93$), HFSR and diarrhoea were the most commonly reported AEs responsible for dose reduction (7.7% for both) or interruption (4% and 7%, respectively). Hypertension resulted in dose reduction in 5 patients (3%) and dose interruption in 6 patients (4%). No dose modifications occurred because of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations.

3.6. Initial presentation of AEs by cycle

AEs of any grade tended to develop early during the treatment with sorafenib (Fig. 2). Of the 17 evaluated by the cycle, 14 AEs presented more frequently in the first cycle than in any other cycle thereafter, until the decreasing sample size of patients

Table 1 – Baseline characteristics of patients who received sorafenib in TARGET.

No. of patients (%)	Long-term treatment subpopulation (n = 169)	Patients randomized to sorafenib arm (N = 451)
Sex		
Male	120 (71)	315 (70)
Female	49 (29)	136 (30)
Age, years		
Median (range)	60 (19–80)	58 (19–86)
<65 years	108 (64)	305 (68)
⩾65 years	61 (36)	146 (32)
Median time since diagnosis, years (range)	2.3 (0–19)	1.7 (0–19)
Baseline ECOG PS		
0	96 (57)	219 (49)
1	71 (42)	223 (49)
2	1 (1)	7 (2)
Missing	1 (1)	2 (0)
MSKCC category		
Favourable	113 (67)	233 (52)
Intermediate	56 (33)	218 (48)
Number of metastatic sites		
1	30 (18)	62 (14)
2	53 (31)	131 (29)
3	46 (27)	114 (25)
4	26 (15)	88 (20)
5 or more	14 (8)	54 (12)
Missing data	0 (0)	2 (0)
Baseline metastatic site		
Lung	125 (74)	348 (77)
Liver	39 (23)	116 (26)
Bone	31 (18)	96 (21)
Prior nephrectomy	162 (96)	422 (94)
Prior cytokine therapy	141 (83)	374 (83)
Prior medical history[a]		
Hypertension[b]	78 (46)	183 (41)
Coronary artery or ischaemic heart disease	22 (13)	53 (12)
High cholesterol[c]	21 (12)	53 (12)
Diabetes[d]	18 (11)	56 (12)
Anaemia	10 (6)	39 (9)

TARGET, Treatment Approaches in Renal cancer Global Evaluation Trial; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MSKCC, Memorial Sloan-Kettering Cancer Center; and NEC, not elsewhere classified.

[a] Using *Medical Dictionary for Regulatory Activities* (MedDRA) version 9.1 terminology.

[b] Per MedDRA terminology, vascular hypertensive disorder.

[c] Per MedDRA terminology, elevated cholesterol, elevated triglycerides, and hyperlipidaemias NEC.

[d] Per MedDRA terminology, diabetes mellitus, including subtypes.

at risk permitted single events to exceed the presentation rate in the first cycle. In the first cycle, 38% of the patients experienced rash/desquamation, 29% of the patients experienced HFSR, 23% of the patients experienced diarrhoea, 14% of the patients experienced fatigue, and 12% of the patients experienced hypertension. In the following cycles, fewer new cases were reported of rash/desquamation (11%, 5%, and 2% for cycles 2, 3, and 4, respectively), HFSR (16%, 3%, and 1% for cycles 2, 3, and 4, respectively), and hypertension (5%, 5%, and 2% for cycles 2, 3, and 4, respectively), and these AEs seldom (<5% of patients at risk) developed later in the therapy. Diarrhoea and fatigue continued to be reported at varying frequencies in the later cycles, albeit at reduced rates of initial presentation; the 3 cycles with the highest rates of subsequent diarrhoea were cycle 2 (21%), cycle 3 (16%), and cycle 10 (11%), and for fatigue were cycle 15 (9%), cycle 3 (6%), and cycle 2 (6%). These AEs presented with a severity of grade 3/4 infrequently (Supplementary Fig. 1), and tended to emerge during the cycles with high incidence of any grade AE, such that grade 3/4 HFSR developed most frequently in early cycles (cycles 1–5 and 7) and grade 3/4 diarrhoea was observed in cycles 4, 5, and 11.

Exceptions to this early-onset trend were anaemia, cardiac ischaemia/infarction, and left ventricular systolic dysfunc-

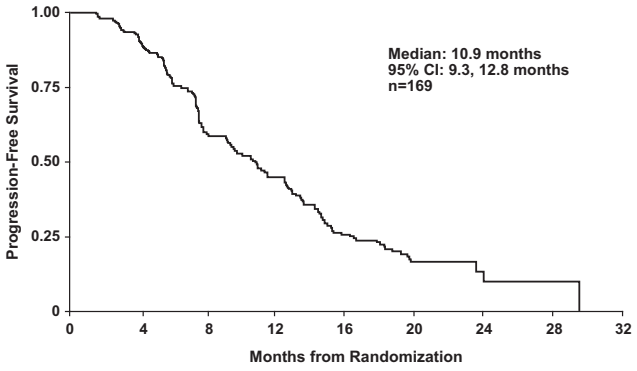

Fig. 1 – Progression-free survival in patients who received sorafenib for >1 year.

Table 2 – Response rates in patients treated with sorafenib for >1 year.

Best response[a]	No. of patients (n = 169)	% of patients (95% CI)
Overall response (CR + PR)	38	23 (16.4, 29.5)
CR	2	1 (0.1, 4.2)
PR	36	21 (15.4, 28.3)
SD	126	75 (67.3, 80.9)
PD	5	3 (1.0, 6.8)
DCR[b]	156	92 (87.2, 95.8)

CI, confidence interval; CR, complete response; DCR, disease control rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; and SD, stable disease.

[a] CR and PR were confirmed.

[b] Defined as the proportion of patients who achieved confirmed CR, PR, or SD on the basis of RECIST that was maintained for ⩾28 d following first demonstration of response.

tion, with an overall low incidence (5%, 2%, and 1%, respectively). As shown in Fig. 2, anaemia and cardiac ischaemia/infarction were reported later in the treatment, but no particular pattern was evident. Left ventricular systolic dysfunction was experienced by 1 patient (9% of patients at risk) in cycle 17.

3.7. *Overall incidence of AEs by cycle*

Overall incidence rates of AEs of any grade per cycle during the course of the therapy are reported in Fig. 3, and the overall incidence of AEs of grade 3/4 are reported in Supplementary Fig. 2. As expected from the early presentation of dermatologic AEs, incidence rates were moderately high in the early cycles for rash/desquamation (37%, 39%, and 36% in cycles 1, 2, and 3, respectively) and HFSR (29%, 37%, and 35% in cycles 1, 2, and 3, respectively). The incidence of HFSR decreased during each following cycle. Rash/desquamation was reported less frequently in each cycle until cycle 10, in which an incidence of 12% was reported, which was slightly higher than the 11% in cycle 9, and there was another rise in incidence from cycles 13 to 16, culminating in 20% of the patients experiencing this AE. In cycles 17 and 18, 9% and 0% of patients reported rash/desquamation. Incidence rates of diarrhoea rose during the early cycles (23%, 29%, 39%, and 39% in cycles 1, 2, 3, and 4, respectively), and the percentage of patients experiencing diarrhoea remained moderately high over the course of therapy, with a range of 29% of the patients in cycle 18 to 51% of patients in cycle 12. The incidence varied little over time for fatigue (range, 13% in cycle 14 to 24% in cycle 15) and hypertension (range, 8% in cycle 16 to 17% in cycle 3).

Of the AEs with later presentations, anaemia was first noted in 1.2% of the patients during cycle 4; in the following cycles the range of incidence was 0% in cycle 15 to 14% (1 of the 7 patients at risk) in cycle 18. Cardiac

Table 3 – Treatment-related adverse events occurring in ⩾10% of patients who received sorafenib >1 year.

	No. of patients (%)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any	160 (95)	21 (12)	81 (48)	49 (29)	9 (5)
Diarrhoea	125 (74)	52 (31)	69 (41)	4 (2)	0
Rash/desquamation	86 (51)	54 (32)	31 (18)	1 (1)	0
HFSR	83 (50)	33 (20)	38 (23)	12 (7)	0
Alopecia	66 (39)	62 (37)	4 (2)	0	0
Fatigue	64 (38)	36 (21)	24 (14)	4 (2)	0
Hypertension	43 (25)	9 (5)	25 (15)	8 (5)	1 (1)
Pruritus	37 (22)	30 (18)	6 (4)	1 (1)	0
Nausea	35 (21)	27 (16)	8 (5)	0	0
Flushing	20 (12)	18 (11)	2 (1)	0	0
Dry skin	29 (17)	23 (14)	6 (4)	0	0
Anorexia	29 (17)	16 (10)	12 (7)	1 (1)	0
Sensory neuropathy	28 (17)	20 (12)	8 (5)	0	0
Weight loss	26 (15)	8 (5)	14 (8)	4 (2)	0
Vomiting	23 (14)	16 (10)	7 (4)	0	0
Oral mucositis	17 (10)	13 (8)	4 (2)	0	0

HFSR, hand–foot skin reaction.

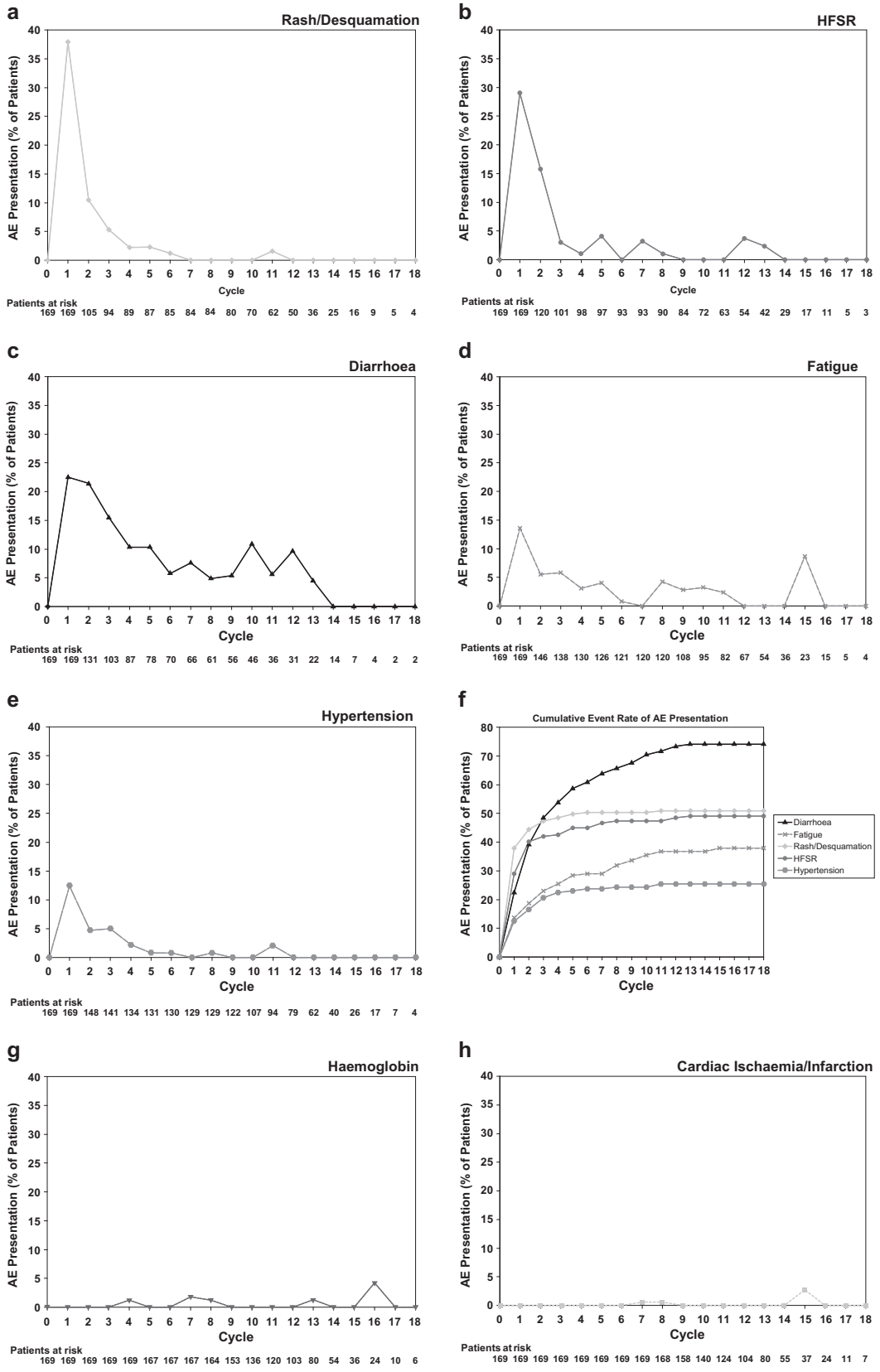

Fig. 2 – (a–h) Rates of initial presentation per cycle of treatment-related AEs of any grade occurring in patients treated with sorafenib for >1 year.

ischaemia/infarction was reported once each in cycles 7, 8, and 15, mirroring the presentation rates. The incidence of grade 3/4 AEs by interval was similar to the presentation rates for grade 3/4 AEs.

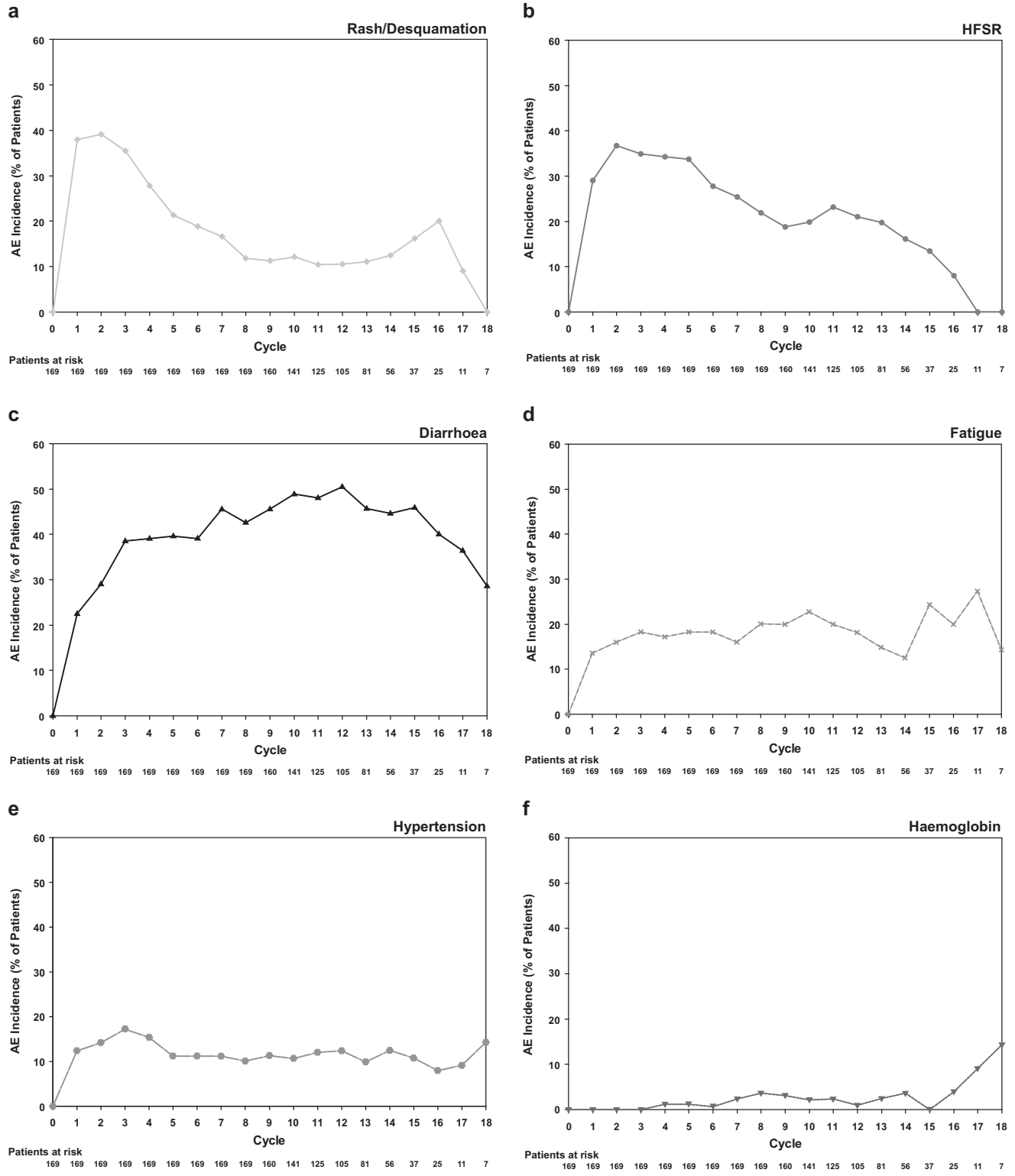

Fig. 3 – (a–f) Rates of overall incidence per cycle of treatment-related AEs of any grade occurring in patients treated with sorafenib for >1 year.

4. Discussion

This post hoc exploratory subanalysis describes 169 patients who remained on sorafenib for >1 year while enrolled in TARGET. Sorafenib was associated with a long PFS and was well tolerated during extended courses of therapy. Notably, treatment-related AEs tended to emerge early in the treatment, with few initial presentations occurring in later cycles. However, these results should be viewed with some caution because of the small patient population and potential bias

in the selection of patients who received sorafenib for >1 year. Despite few data on the long-term administration of sorafenib and other targeted therapies, this retrospective analysis provides valuable insights that may help guide clinical decision making.

It is important to note that this long-term treatment subpopulation included patients who tended to have a better baseline health status than the full study population (ECOG PS 0, 56.8% versus 48.6%, respectively; favourable MSKCC score, 67% versus 52%, respectively).[5] While other baseline characteristics were similar to the sorafenib arm of TARGET, the baseline health status is a substantial factor in the prognosis for advanced RCC, and so the subpopulation described here included a greater proportion of patients with good prognosis than the randomised population. Moreover, this subpopulation was defined by the duration of therapy of $\geqslant$12 months. Patients continued on sorafenib for an extended period if they experienced a clinical response to sorafenib, and correspondingly, the DCR was higher in this subpopulation than in all patients in the sorafenib arm (92% versus 62%), primarily due to the higher proportion of the responders (21% versus 10%).

Patients in the long-term treatment subpopulation generally tolerated sorafenib well. The incidence of treatment-related AEs of any grade was 95%. The high incidence of AEs may reflect the prolonged exposure to sorafenib (>1 year). It is reasonable to predict that the long-term administration of a drug will lead to a higher cumulative incidence of AEs. No unexpected toxicities occurred, and most AEs were grade 1 or 2 in severity. The most frequently reported AEs were diarrhoea, rash/desquamation, HFSR, alopecia, and fatigue. Altogether, these data suggest that the long-term administration of sorafenib is associated with acceptable toxicity.

Treatment-related AEs tended to present most frequently in the first cycle, and the incidence patterns of AEs of any grade varied in later cycles. The rates of initial presentation and overall incidence of HFSR and rash/desquamation dropped substantially after the first cycle, suggesting that patients who do not experience these AEs early in the course of the treatment are unlikely to develop them later. Diarrhoea, fatigue, and anaemia were the only AEs that increased in incidence over the course of the therapy. Although the increases or decreases of severity cannot be determined from these analyses, the rates of the initial presentation of AEs grade 3/4 did not suggest that AEs became more severe over time. Despite the prevalence of hypertension in this subpopulation, cardiovascular AEs occurred stochastically over the treatment cycles, and these SAEs were rare. In a recent observational study of the cardiotoxicity of sorafenib and sunitinib, Schmidinger and colleagues reported that some patients who experienced cardiovascular AEs were asymptomatic without the regular assessments of biochemical indications and echocardiogram changes.[16] It is important to note that TARGET was not designed to evaluate cardiotoxicity, and so cardiac function was not routinely monitored; the safety profile presented here may underestimate the prevalence of these AEs. Monitoring patients with a history of cardiovascular disease is recommended with the use of all antiangiogenic therapies.[13]

The decision to treat the patients enrolled in TARGET post-progression was made by the investigator based on the improvements in the health status of the patient, despite the growth of the primary lesion as assessed by RECIST. The results of this subanalysis suggest that therapy beyond disease progression may be feasible for some patients if there is a clinical benefit prior to reaching the PFS time point. This observation complements the findings of recent dose-escalation studies. Two phase II trials have investigated the efficacy of the dose escalation of sorafenib post-progression.[17,18] Both the studies reported that progression can be delayed by increasing sorafenib dosage after documented progression. As seen in this subanalysis of TARGET, no unexpected AEs occurred during the extended courses of sorafenib therapy.[17,18] Indeed, Escudier and colleagues reported a decrease in the AE incidence during the period of treatment post-progression, potentially reflecting successful AE management during the first course of the treatment.[18] Sequential therapy with targeted agents has become a standard practise in the treatment of advanced RCC, whereby a second drug is prescribed after disease progression on the first.[19] The data presented here and in dose-escalation studies suggest that long-term sorafenib therapy, including continued therapy post-progression, is possible.

The results of this subanalysis demonstrate that sorafenib is well tolerated during long-term administration. One limitation of this study is that it was a post hoc exploratory analysis rather than a prospective trial; TARGET was not designed to evaluate long-term safety, and these post-crossover safety analyses are descriptive. Nonetheless, sorafenib treatment for >1 year did not lead to unexpected AEs, indicating that there is no cumulative toxicity. AEs presented early in the course of treatment, and did not portend future intolerance to sorafenib. Instead, treatment through toxicity, accompanied by management of AEs, may allow patients to achieve tumour control with sorafenib. Results of this subanalysis advocate for management of AEs with early recognition and treatment if they develop. Patients may then be able to continue sorafenib therapy through the early cycles and experience the drug's full potency to achieve disease control over the course of therapy. Moreover, the data suggest that the option of continued therapy post-progression is possible. Clinical trials designed to evaluate long-term treatment safety with sorafenib and other TKIs are needed to validate these observations.

Source of support

Bayer HealthCare sponsored the study design, administration of treatment, and statistical analysis of the trial. Data were managed in parallel by the sponsor and the principal investigators. Bayer HealthCare funded the writing assistance in the form of preparation of the manuscript, references, figures, tables, collation of author comments, editing, and administrative support.

Conflict of interest statement

T.E.H. received consultancy fees, lecture fees and/or honoraria from Bayer HealthCare, Pfizer, Wyeth, GlaxoSmithKline, and Genentech. J.B. has received consulting fees from, lectur-

ing fees from and/or served on advisory boards for Bayer HealthCare, Pfizer, Roche, Wyeth, and Novartis. C.P. received lecture fees from Bayer HealthCare, Pfizer, Roche, Wyeth, and Novartis and his institution received a research grant from Bayer HealthCare. C.S. has received lecture fees and research grants from and has served on an advisory board for Bayer HealthCare. M.S. received consulting fees and/or served on advisory boards from Bayer HealthCare, and his institution received research funding from Bayer HealthCare. A.N. and S.A. are employed by Bayer HealthCare. R.B. received honoraria and/or lecture fees from Bayer HealthCare, Pfizer, Novartis, Genentech, GlaxoSmithKline. T.E. has received consulting fees, lecturing fees and/or honoraria from Bayer HealthCare, Wyeth, Pfizer, Roche, AstraZeneca, Novartis, and Roche; T.E. has research grants pending from Bayer HealthCare and Pfizer. B.E. has received consulting fees from Bayer HealthCare, Roche, GlaxoSmithKline, and Novartis.

Acknowledgements

We acknowledge the contributions of the other TARGET investigators. We thank Katherine Stevens of Ogilvy Healthworld for assisting with the manuscript preparation. This study and the medical writing support were sponsored by Bayer HealthCare and Onyx Pharmaceuticals.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2010.06.121.

REFERENCES

1. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001;**345**:1655–9.
2. Mickisch GH, Garin A, Van PH, de PL, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* 2001;**358**:966–70.
3. Maranchie JK, Vasselli JR, Riss J, et al. The contribution of VHL substrate binding and HIF1-alpha to the phenotype of VHL loss in renal cell carcinoma. *Cancer Cell* 2002;**1**:247–55.
4. Motzer RJ, Rini BI, Bukowski RM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;**356**:125–34.
5. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;**356**:125–34.
6. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;**356**:115–24.
7. Escudier B, Eisen T, Stadler WM, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon alfa-2a in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;**27**:1280–9.
8. Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma. *Lancet Oncol* 2009;**10**:757–63.
9. Hutson TE, Davis ID, Machiels JH, et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2010;**28**:475–80.
10. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010;**28**:1061–8.
11. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004;**64**:7099–109.
12. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III Treatment Approaches in Renal cancer Global Evaluation Trial. *J Clin Oncol* 2009;**27**:3312–8.
13. Hutson TE, Figlin RA, Kuhn JG, Motzer RJ. Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies. *Oncologist* 2008;**13**:1084–96.
14. Smith W, Kipnes MS, Marbury TC, et al. Effects of renal impairment on the pharmacokinetics and safety of sorafenib. *Eur J Cancer Suppl* 2009;**7**:433.
15. Eisen T, Oudard S, Szczylik C, et al. Sorafenib for older patients with renal cell carcinoma: subset analysis from a randomized trial. *J Natl Cancer Inst* 2008;**100**:1454–63.
16. Schmidinger M, Zielinski CC, Vogl UM, et al. Cardiac toxicity of sunitinib and sorafenib in patients with renal cell carcinoma. *J Clin Oncol* 2008;**26**:5204–12.
17. Amato RJ, Harris P, Dalton M, et al. A phase II trial of intrapatient dose-escalated sorafenib in patients (pts) with metastatic renal cell cancer (MRCC). *J Clin Oncol* 2007;**25**(18S):5026.
18. Escudier B, Szczylik C, Hutson TE, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon alfa-2a in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;**27**:1280–9.
19. Rini BI, Atkins MB. Resistance to targeted therapy in renal-cell carcinoma. *Lancet Oncol* 2009;**10**:992–1000.