Sorafenib dose escalation in treatment-naïve patients with metastatic renal cell carcinoma: a non-randomised, open-label, Phase 2b study

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Objective

To assess the efficacy and safety of sorafenib dose escalation in metastatic renal cell carcinoma (mRCC).

Patients and Methods

Intra-patient dose escalation may enhance the clinical benefit of targeted anticancer agents in metastatic disease. In this non-randomised, open-label, Phase 2b study, treatment-naïve patients with mRCC were initially treated with the standard oral sorafenib dose [400 mg twice daily (BID)]. Two dose escalations were planned, each 200 mg BID after 28 days at the prior level. Dose reductions, interruptions, or delayed escalations were used to manage adverse events (AEs). The primary endpoint was objective response rate (ORR) in the modified intent-to-treat (mITT) population, which comprised patients with ≥6 months of treatment including ≥4 months of therapy at their highest tolerated dose. Secondary endpoints included progression-free survival (PFS) and safety.

Results

In all, 83 patients received sorafenib. The dose received for the longest duration was 400, 600, and 800 mg BID in 48.2%, 15.7%, and 24.1% of patients, respectively. The ORR was 44.4% [n = 8/18; 95% confidence interval (CI) 21.5–69.2] and 17.9% (n = 12/67; 95% CI 9.6–29.2) in the mITT and ITT populations, respectively. The median (95% CI) PFS was 7.4 (6.0–11.7) months (ITT). The most common AEs of any grade were hand–foot skin reaction (66.3%) and diarrhoea (63.9%).

Conclusion

Sorafenib demonstrated clinical benefit in treatment-naïve patients with mRCC. However, relatively few patients could sustain doses of >400 mg BID. There was evidence that, where tolerated, escalation from the standard sorafenib dose may have enhanced clinical benefit. However, this study does not support dose escalation for most patients with treatment-naïve mRCC. Alternative protocols for sorafenib dose escalation could be explored.

Introduction

The advent of molecularly targeted agents brought welcome advances in the treatment of metastatic RCC (mRCC). However, more effective approaches to this ultimately incurable disease are needed. One strategy is intra-patient dose escalation of agents that have demonstrated efficacy and tolerability.

Sorafenib, an oral inhibitor of several kinases involved in tumour angiogenesis and cell proliferation, is approved in differentiated thyroid carcinoma, hepatocellular carcinoma, and advanced/mRCC [1-6]. The pivotal TARGET trial in patients pre-treated with cytokine therapy demonstrated efficacy of sorafenib 400 mg twice daily (BID); this subsequently became the approved regimen [3-6].

Attempts to enhance clinical outcome investigated sorafenib doses >400 mg BID [7-9]. A Phase 2 study in mRCC in which ~50% of patients had received prior systemic therapy but no tyrosine kinase inhibitor escalated the sorafenib dose at 28-day intervals to 600 mg BID [in 92.9% of patients (n = 39/42)], then 800 mg BID [in 73.8% of patients (n = 31/42)] [9]. The objective response rate (ORR)

was 47.7% (n = 21/44) and median progression-free survival (PFS) was 8.4 months [9]. These outcomes compared favourably with those of TARGET.

Further investigation of sorafenib dose escalation was therefore warranted. In the present study, we report the efficacy, safety, and tolerability from an open-label, Phase 2b study of planned sorafenib dose escalation in treatment-naïve patients with mRCC.

Patients and Methods

Study Design and Patients

This non-randomised, open-label, uncontrolled, international, multicentre, Phase 2b study (ClinicalTrials.gov NCT00618982) recruited patients aged ≥18 years with: histologically/cytologically confirmed metastatic clear cell RCC; no prior systemic therapy for RCC; Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1; intermediate or good prognosis according to the Memorial Sloan-Kettering Cancer Center scale [10]; ≥1 measurable lesion by CT or MRI according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.0; life expectancy of ≥12 weeks; prior nephrectomy; and adequate bone marrow, liver, and renal function assessed within 7 days prior to study treatment. Prior palliative radiotherapy to non-targeted metastatic lesions according to RECIST was permitted.

Exclusion criteria included: history of cardiac disease (congestive heart failure >New York Heart Association class 2); acute coronary disease (myocardial infarction >6 months before study entry was allowed); cardiac arrhythmias requiring anti-arrhythmic therapy (β-blockers or digoxin were permitted); or uncontrolled hypertension; history of HIV infection or chronic hepatitis B or C; active clinically serious infections >Grade 2; symptomatic metastatic brain or meningeal tumours; seizure disorders requiring medication; history of organ allograft; evidence or history of bleeding diathesis; deep vein thrombosis and/or pulmonary embolus within 12 months of treatment initiation; delayed healing of wounds, ulcers, or bone fractures; pre-existing thyroid abnormality; undergoing renal dialysis; previous or concurrent cancer distinct in primary site or histology from mRCC (except cervical carcinoma in situ, treated basal cell carcinoma, non-muscle-invasive bladder cancer, or any cancer curatively treated >3 years prior to study entry); pregnancy/breastfeeding; inability to swallow oral medications; any prior systemic anticancer therapy; major surgery within 4 weeks prior to study entry; radiotherapy within 3 weeks of study drug initiation; biological response modifiers, e.g. granulocyte colony stimulating factor (G-CSF), within 3 weeks prior to study entry; or autologous bone marrow transplant or stem cell rescue within 4 months of study entry.

All patients provided written informed consent, and study approval was obtained from ethics committees (Table S1). The study was conducted in accordance with the World Medical Association Declaration of Helsinki, the International Conference on Harmonization guideline E6 for Good Clinical Practice, and local ethical and legal requirements.

Treatment

The initial dose was oral sorafenib 400 mg BID. Two dose escalations were planned: to 600 mg BID after 28 days at the starting dose, then to 800 mg BID after another 28 days. The occurrence of any symptomatic adverse event (AE) ≥Grade 3 (except nausea or vomiting) prevented dose escalation until the event resolved to Grade 1. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, investigator's decision, or study end. Dose delays or reductions to 400 or 200 mg daily were allowed to manage AEs (200 mg daily dose given as 400 mg every other day or 200 mg once daily). Dose modification or delay due to hypertension or dermatological, haematological, and non-haematological AEs was permitted according to specific criteria (Tables S2–S6).

Concomitant therapies were allowed: palliative radiotherapy to ≤10% of the patient's bone marrow provided that a target lesion was not irradiated and there was no progressive disease; G-CSF and other haemopoietic growth factors to manage acute toxicity, and secondary (not primary) prophylaxis with erythropoietin, providing these did not replace a required sorafenib dose reduction; other palliative/supportive care, including bisphosphonates.

Assessments

Efficacy analyses were performed in the intent-to-treat (ITT) population (all patients who received ≥1 sorafenib dose and had ≥1 valid efficacy evaluation post-baseline). The primary endpoint was the ORR (complete or partial response) at 6 months in patients with ≥4 months of therapy at the highest tolerated dose; this was analysed in the modified ITT (mITT) population (subgroup treated for ≥6 months with ≥4 months at their highest tolerated sorafenib dose). Secondary endpoints included PFS, time to progression (TTP), safety and tolerability, and pharmacokinetics. The safety population included all patients who received ≥1 sorafenib dose and for whom post-baseline data were available.

Tumour response and progression were assessed by central, independent, radiological review every 8 weeks using RECIST v1.0 [11]. Objective responses or stable disease were confirmed at the next scheduled scan. PFS was assessed from the start of study medication to the first radiological or clinical progression, or death. The TTP was measured from the start of study medication to the first radiological or clinical progression. AEs were assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0 [12]. Pharmacokinetic samples (6 mL) were collected on day 28 of the first completed cycle at each dose level at pre-dose and 2, 4, 6, 8, 10, and 12 h post-dose time points. Samples to measure plasma levels of sorafenib and its metabolites (M2, M4, and M5) were drawn on day 28 of the first cycle at each dose level.

Determination of Sample Size

A sample size of 80 patients was chosen in order to get a 95% CI ± 10% for a response rate of ~30% (nQuery version 6.1 module POCO-1).

Results

Patients

The first patient was treated on 4 February 2008; the last patient visit was 13 January 2011; and the data collection limit was 6 August 2012. In all, 89 patients enrolled at 19 centres in France, UK, Germany, Italy, and Poland. Of these, 83 patients received sorafenib and were included in the safety population (Fig. S1). The ITT and mITT populations included 67 and 18 patients, respectively. Of the 49 ITT patients excluded from the mITT population, 32 (65.3%) and 14 (28.6) discontinued sorafenib due to disease progression and toxicity, respectively (Table S7).

The ITT subgroups according to the sorafenib dose received for the longest duration showed broadly similar baseline demographics (Table 1). The mean time since diagnosis was 2.0, 0.7, and 2.3 years with 400, 600, and 800 mg BID dose, respectively.

Table 1. Baseline demographic and clinical characteristics

	Safety population	ITT population			
	Overall (*n*= 83)	**Overall (*n* = 67)**	**400 mg BID*(*n* = 25)**	**600 mg BID*(*n* = 12)**	**800 mg BID*(*n* = 20)**
Median (range) age, years	61 (33–80)	62 (33–80)	64 (44–80)	59 (33–78)	57 (39–72)
Male, *n* (%) or *n*/*N*	54 (65.1)	44 (65.7)	15 (60.0)	9/12	15 (75.0)
ECOG PS, *n* (%) or *n*/*N*					
0	49 (59.0)	40 (59.7)	14 (56.0)	7/12	13 (65.0)
1	34 (41.0)	27 (40.3)	11 (44.0)	5/12	7 (35.0)
Disease stage, *n* (%) or *n*/*N*					
III	1 (1.2)	1 (1.5)	0	0	0
IV	82 (98.8)	66 (98.5)	25 (100.0)	12/12	20 (100.0)
Clinical/radiological status at entry, *n* (%) or *n*/*N*					
Stable disease	15 (18.1)	12 (17.9)	4 (16.0)	2/12	2 (10.0)
Progressive disease	68 (81.9)	55 (82.1)	21 (84.0)	10/12	18 (90.0)

Mean (SD) time since initial diagnosis†, years	2.1 (3.1)	2.0 (3.1)	2.0 (3.9)	0.7 (0.7)	2.3 (3.0)
Number of metastatic lesions, *n* (%) or *n*/*N*					
1	14 (16.9)	0	0	0	0
≥2	69 (83.1)	67 (100.0)	25 (100.0)	12/12	20 (100.0)
Metastatic sites, *n* (%) or *n*/*N*					
Lung	53 (63.9)	51 (76.1)	20 (80.0)	11/12	14 (70.0)
Lymph nodes	33 (39.8)	33 (49.3)	10 (40.0)	7/12	11 (55.0)
Liver	25 (30.1)	25 (37.3)	8 (32.0)	4/12	9 (45.0)
Bone	16 (19.3)	16 (23.9)	9 (36.0)	2/12	3 (15.0)
Prior therapy for RCC, *n* (%) or *n*/*N*					
Surgery	83 (100.0)	67 (100.0)	25 (100.0)	12/12	20 (100.0)
Radiotherapy	12 (14.5)	10 (14.9)	4 (16.0)	3/12	1 (5.0)
Systemic anticancer therapy‡	3 (3.6)	2 (3.0)	1 (4.0)	0/12	0

*Dose taken for the longest duration while in the study; 10 patients treated at doses <400 mg BID are not included because of small sample sizes; †These data were unavailable for one patient in each of the overall safety population (n = 82) and the overall ITT population (n = 66) [in the 400 mg BID group (n = 24)]; ‡Three patients received prior anticancer therapy with endocrine therapy (n = 2) and an immunostimulant (n = 1). These treatments were not considered protocol violations.

Treatment Duration and Doses Received

In the safety population, the median (range) treatment duration was 225 (7–1072) days, mean (SD) daily dose was 902 (364) mg/day, and the median (range) duration of follow-up was 252 (14–1 071) days. The maximum dose reached was 400 mg BID in 31 (37.3%) patients, 600 mg BID in 12 (14.5%) patients, and 800 mg BID in 40 (48.2%) patients. The dose [median (range) duration] received for the longest duration was 400 mg BID in 40 (48.2%) patients [29.5 (7–855) days]; 600 mg BID in 13 (15.7%) patients [164 (62–681) days]; 800 mg BID in 20 (24.1%) patients [177.5 (56–956) days]; 400 mg daily in seven (8.4%) patients [434 (122–764) days]; and 400 mg every other day in three (3.6%) patients [332 (136–675) days].
Efficacy

In the mITT population, all patients had partial response (n = 8/18) or stable disease (n = 10/18) (Table 2A). The primary efficacy endpoint, the ORR, was 44.4% (95% CI 21.5–69.2). In the ITT population, the ORR was 17.9% (n = 12/67) (95% CI 9.6–29.2) (Table 2B). Tumour shrinkage occurred in 18/25 (72.0%), (9/12) 75.0%, and 17/20 (85.0%) of patients in the 400, 600, and 800 mg BID groups, respectively (Fig. 1).

Table 2. Tumour response and progression-free survival (PFS) in the modified intent-to-treat (mITT) (A) and ITT (B) populations, assessed by independent central review

	Overall	**200 mg Daily*, †**	**400 mg OD***	**400 mg BID***	**600 mg BID***	**800 mg BID***
(A) **mITT**						
N	18	2	5	1	2	8
Partial response, *n* (%) or *n*/*N*	8 (44.4)	0/2	2/5	1/1	1/2	4/8
Stable disease, *n* (%) or *n*/*N*	10 (55.6)	2/2	3/5	0/1	1/2	4/8
Progressive disease, *n* (%) or *n*/*N*	0	0/2	0/5	0/1	0/2	0/8
Response rate‡, % (95% CI)	44.4 (21.5–69.2)	0 (0–84.2)	40.0 (5.3–85.3)	100.0 (2.5–100.0)	50.0 (1.3–98.7)	50.0 (15.7–84.3)
(B) **ITT**						
N	67	3	7	25	12	20
Partial response, *n* (%) or *n*/*N*	12 (17.9)	0/3	2/7	1 (4.0)	2/12	7 (35.0)
Stable	46 (68.7)	3/3	5/7	15 (60.0)	10/12	13 (65.0)

	Overall	200 mg Daily*, †	400 mg OD*	400 mg BID*	600 mg BID*	800 mg BID*
disease, *n* (%) or *n*/*N*						
Progressive disease, *n* (%) or *n*/*N*	9 (13.4)	0/3	0/7	9 (36.0)	0/12	0
Response rate‡, % (95% CI)	17.9 (9.6–29.2)	0 (0–70.8)	28.6 (3.7–71.0)	4.0 (0.1–20.4)	16.7 (2.1–48.4)	35.0 (15.4–59.2)
Median (95% CI) PFS, months	7.4 (6.0–11.7)	ND§	ND§	3.7 (1.8–9.7)	7.4 (6.3–12.0)	8.5 (5.5–14.9)
Progression-free at 6 months, % or *n*/*N*	62.3	ND§	ND§	49.1	9/12	58.6
Progression-free at 12 months, % or *n*/*N*	33.4	ND§	ND§	24.6	3/12	39.1

No complete responses were recorded. OD, once daily; ND, not determined. *Dose taken for the longest duration while in the study. †200 mg daily dose was received as 400 mg every other day or 200 mg once daily. ‡Response rate defined as complete response + partial response. §These data were not determined due to the small sample sizes for these subgroups.

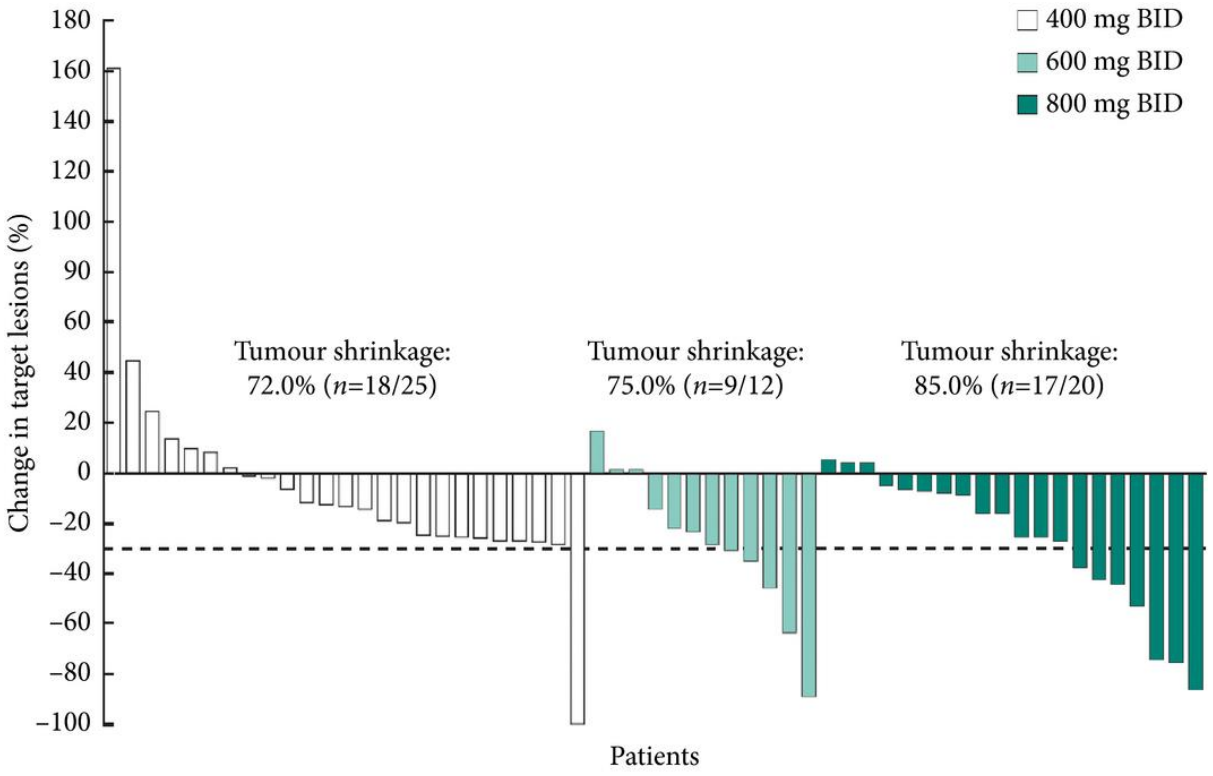

Figure 1.
Maximum tumour shrinkage in individual patients (% change from baseline in target lesions by independent assessment) according to the dose received for the longest duration in the study [intent-to-treat (ITT) population]. Dotted line represents the threshold for response using Response Evaluation Criteria in Solid Tumors (RECIST) v1.0. Maximum tumour shrinkage for patients in the ITT population who received doses of 400, 600, or 800 mg/day twice daily (BID) for the longest duration while in the study were included as long as the independent central reviewer could establish a best response.

In the ITT population, the overall median PFS was 7.4 months (95% CI 6.0–11.7) (Table 2B and Fig. 2 [3]); 62.3% and 33.4% of patients were progression free at 6 and 12 months, respectively. The median (95% CI) PFS was 3.7 (1.8–9.7), 7.4 (6.3–12.0), and 8.5 (5.5–14.9) months for the 400, 600, and 800 mg BID groups, respectively (ITT). The TTP results were identical to those for PFS, because no deaths occurred before disease progression was observed.

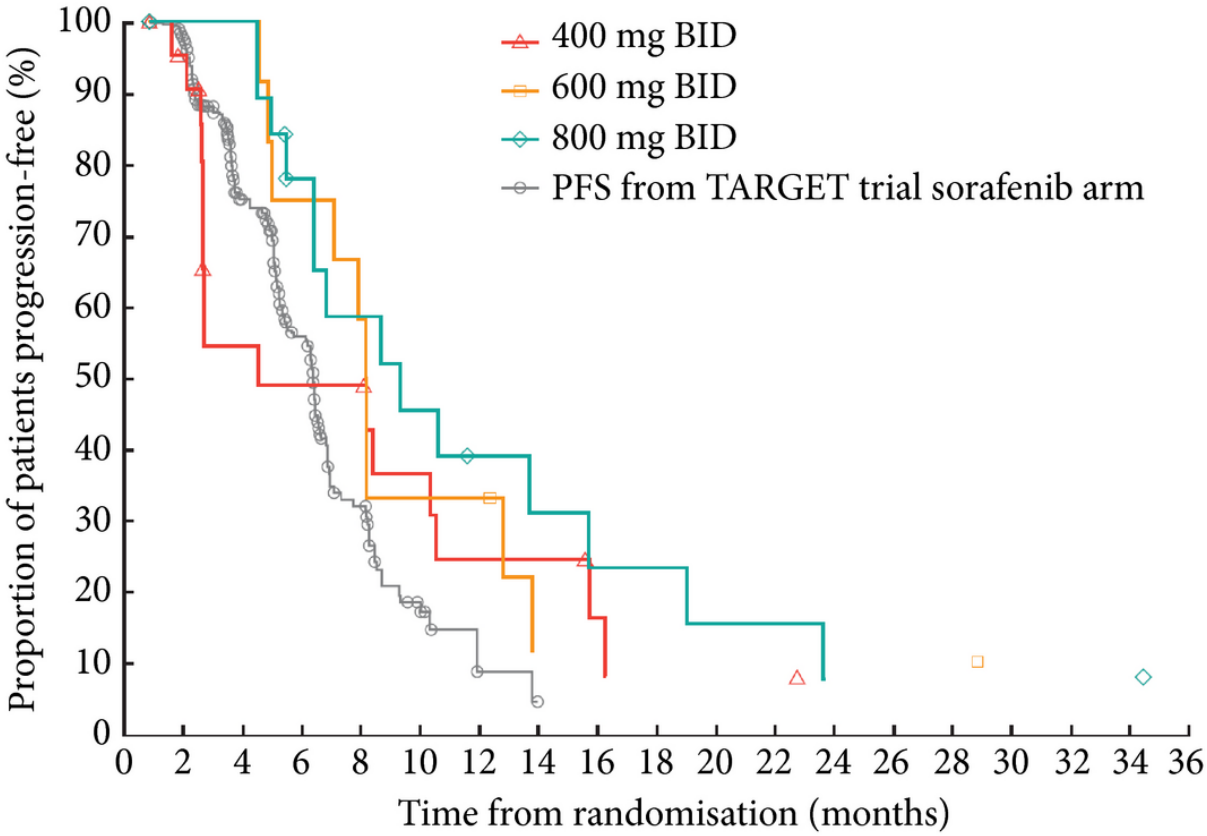

Figure 2.

Kaplan–Meier graph showing progression-free survival (PFS) by independent central assessment according to the dose received for the longest duration in the study [intent-to-treat (ITT) population]. The PFS curve from the Phase 3 trial of sorafenib for treatment of metastatic renal cell carcinoma (mRCC) (TARGET) is shown for comparison [3].

Safety

All 83 patients reported at least one treatment-emergent AE (TEAE). The most common TEAEs of any grade were hand–foot skin reaction (HFSR; 66.3%), diarrhoea (63.9%), rash/desquamation (56.6%), fatigue (54.2%), and hypertension (48.2%) (Table 3). One patient (1.2%) had Grade 2 proteinuria. Most patients (90.4%; *n* = 75) had at least one ≥Grade 3 event. The most common Grade 3 events were HFSR (25.3%), fatigue (15.7%), hypophosphataemia (15.7%), and rash/desquamation (13.3%) (Table 3). Two patients had Grade 3 renal failure. Apart from hyponatraemia and elevated lipase [both two patients (2.4%)], Grade 4 events occurred in individual patients only (Table 3).

Table 4 summarises the TEAEs by dose at first occurrence. Most patients (91.6%) had their first AE at 400 mg BID.

Table 3. Incidence of TEAEs by worst grade, occurring in >10% patients at any grade, >5% patients at Grade 3, or >2% patients at Grade 4 (safety population, *N* = 83)

Adverse event	*n* (%)		
	Any grade	Grade 3	Grade 4
Any event	83 (100.0)	61 (73.5)	13 (15.7)
HFSR	55 (66.3)	21 (25.3)	0
Diarrhoea	53 (63.9)	10 (12.0)	1 (1.2)
Rash/desquamation	47 (56.6)	11 (13.3)	0
Fatigue	45 (54.2)	13 (15.7)	1 (1.2)
Hypertension	40 (48.2)	5 (6.0)	0
Alopecia	36 (43.4)	0	0
Mucositis (functional/symptomatic), oral cavity	27 (32.5)	0	0
Dry skin	23 (27.7)	1 (1.2)	0
Nausea	22 (26.5)	0	0
Anorexia	21 (25.3)	1 (1.2)	0
Hypophosphataemia	17 (20.5)	13 (15.7)	1 (1.2)
Vomiting	16 (19.3)	1 (1.2)	0
Pruritus	15 (18.1)	1 (1.2)	0
Fever	14 (16.9)	0	0
Weight loss	14 (16.9)	1 (1.2)	0

Adverse event	*n* (%)		
	Any grade	Grade 3	Grade 4
Dyspnoea	13 (15.7)	1 (1.2)	0
Haemoglobin	12 (14.5)	1 (1.2)	0
Hypothyroidism	12 (14.5)	0	0
Neuropathy: sensory	12 (14.5)	0	0
Pain, abdomen (not otherwise specified)	11 (13.3)	1 (1.2)	0
Taste alteration	11 (13.3)	0	0
Voice changes	11 (13.3)	0	0
Lipase	10 (12.0)	10 (12.0)	2 (2.4)
Pain, back	10 (12.0)	3 (3.6)	0
Constipation	9 (10.8)	0	0
Alanine aminotransferase	7 (8.4)	5 (6.0)	0
Hyponatraemia	5 (6.0)	3 (3.6)	2 (2.4)

Table 4. Incidence of TEAEs (any grade, occurring in >10% of patients in any category) by dose at first occurrence (safety population)

AE	*n*/*N* or *n* (%)				
	200 mg Daily* (*n* = 10)	**400 mg OD (*n* = 38)**	**400 mg BID (*n* = 83)**	**600 mg BID (*n* = 52)**	**800 mg BID (*n* = 40)**
Any event	1/10	5 (13.2)	76 (91.6)	0	1 (2.5)
HFSR	0/10	3 (7.9)	43 (51.8)	5 (9.6)	4 (10.0)
Rash/desquamation	1/10	1 (2.6)	38 (45.8)	5 (9.6)	2 (5.0)
Fatigue	2/10	2 (5.3)	29 (34.9)	4 (7.7)	5 (12.5)
Hypertension	2/10	4 (10.5)	29 (34.9)	2 (3.8)	2 (5.0)
Diarrhoea	1/10	3 (7.9)	21 (25.3)	19 (36.5)	9 (22.5)
Oral mucositis (functional/symptomatic)	1/10	2 (5.3)	19 (22.9)	4 (7.7)	1 (2.5)
Alopecia	1/10	5 (13.2)	16 (19.3)	9 (17.3)	5 (12.5)
Dry skin	1/10	1 (2.6)	13	3 (5.8)	5

AE	*n*/*N* or *n* (%)				
	200 mg Daily* (*n* = 10)	**400 mg OD (*n* = 38)**	**400 mg BID (*n* = 83)**	**600 mg BID (*n* = 52)**	**800 mg BID (*n* = 40)**
			(15.7)		(12.5)
Hypophosphataemia	0/10	1 (2.6)	13 (15.7)	3 (5.8)	0
Nausea	2/10	2 (5.3)	10 (12.0)	3 (5.8)	5 (12.5)
Pruritus	0/10	2 (5.3)	10 (12.0)	2 (3.8)	0
Vomiting	0/10	1 (2.6)	8 (9.6)	2 (3.8)	5 (12.5)
Anorexia	1/10	0	6 (7.2)	8 (15.4)	6 (15.0)
Weight loss	0/10	0	5 (6.0)	2 (3.8)	7 (17.5)
Hypocalcaemia	0/10	0	1 (1.2)	0	5 (12.5)

Data are ordered in decreasing incidence seen in the largest subgroup (400 mg BID). OD, once daily.
*200 mg daily dose was received as 400 mg every other day or 200 mg OD.

Serious TEAEs were reported in 44 (53.0%) patients and most were single occurrences. The most common serious TEAEs, each occurring in three (3.6%) patients, were fatigue, rash/desquamation, gastrointestinal (other), hyponatraemia, and intraoperative injury.

Dose interruptions, reductions, and withdrawals due to AEs occurred in 69 (83.1%), 50 (60.2%), and 36 (43.4%) patients, respectively. Dose interruptions or withdrawals occurred most frequently in patients receiving 400 mg BID vs other doses.

One death was reported, due to cardiopulmonary failure, which was not considered to be related to sorafenib. Another death was reported >30 days after the last study drug dose due to cardiopulmonary failure caused by progressive RCC. In both cases, the sorafenib dose received for the longest duration was 400 mg BID.

Pharmacokinetics

No increase in exposure [area under the curve (AUC) or maximum plasma concentration (Cmax)] for sorafenib or its metabolites (M2, M4, and M5) was observed with increase in dose, indicating a lack of dose proportionality (Table S8).

Discussion

In the present open-label dose-escalation study, sorafenib showed apparent clinical benefit in the ORR and PFS in treatment-naïve patients with mRCC in the mITT population. The ORR for the mITT population (eight of 18 patients, 44.4%) compared favourably to that in other first-line sorafenib trials [3, 8, 13-17], and was similar to that in the Phase 2 dose-escalation study of Amato et al. [9] of 47.7%. These observations suggest that mITT patients may have gained additional benefit from sorafenib dose escalation. However, these results should be interpreted cautiously due to small patient numbers and the fact that, by definition, the mITT population had tolerated sorafenib relatively well (≥4 months at the maximum tolerated dose) and had slow-growing tumours (stayed in the study for ≥6 months). The mITT population may only represent a small proportion of patients with mRCC.

In the ITT population, the median PFS (7.4 months) and ORR (17.9%) fell within the ranges reported in Phase 2/3 studies of first-line standard-dose sorafenib in mRCC (median PFS 5.5–9.1 months; ORR 5.2–30.0%) [3, 8, 13-17]. Therefore, the results of the present study do not support an improved benefit/risk ratio with sorafenib dose escalation up to 800 mg BID in mRCC compared to historical data with sorafenib 400 mg BID. However, comparison of ORR and PFS in different dose groups showed that patients who tolerated higher doses of sorafenib (>400 mg BID) appeared to have enhanced clinical benefit compared with those receiving doses of ≤400 mg BID. However, a meaningful comparison between the dosage groups is limited because the higher-dose groups were enriched with patients who tolerated sorafenib better and whose disease progressed later.

Outcomes in the ITT population appeared inferior to those reported by Amato et al. [9], who followed a similar dose-escalation protocol [9]. This may reflect the fact that sorafenib therapy and dose escalation were less well tolerated in the present study. Of note, the numbers of Grade 3/4 AEs in the Amato et al. study were much lower, allowing a greater proportion of patients to reach and potentially benefit from the 800 mg BID dose. Patients in the Texan Amato et al. [9] study could have been more homogeneous, and different in anthropometric characteristics, compared with our international ITT population.

Dosage groups for pharmacokinetics were not the same as for efficacy (dose received for the longest duration) or safety (dose at first occurrence). Rather, blood for pharmacokinetic analyses was collected on day 28 of the first cycle completed at each dose level. No apparent increase in sorafenib exposure was seen at higher doses. However, patients were not randomised into dose groups, there is large inter-patient variation in sorafenib exposure at the same dose, and incidence of Grade 3/4 AEs has been associated with higher exposure [18, 19]. Patients with low sorafenib exposure may therefore have been over-represented in the high-dose groups, being less prone to severe AEs that

precluded dose escalation. Further confounding interpretation of pharmacokinetic data, samples from patients receiving higher doses were taken at later time points than lower-dose samples, and sorafenib exposure declines over time [19, 20].

No new or unexpected toxicities arose in our present study. Most TEAEs first occurred with the starting dose of sorafenib, 400 mg BID, which is consistent with previous analyses showing that AEs with sorafenib tend to first occur early in treatment [21, 22]. Gastrointestinal disorders were the exception, most often starting with 600 or 800 mg BID. These findings should be interpreted cautiously given that patients were not randomised to dose groups. However, these observations are consistent with data from a sorafenib dose-escalation study in metastatic melanoma, where HFSR and hypertension correlated with exposure, whereas diarrhoea and anorexia correlated with dose level [23]. The small proportion of patients who could sustain the highest dose level and the need for frequent dose reductions and interruptions to manage AEs reflects the difficulties of generally implementing a dose-escalation schedule in this patient population. However, there may be value in exploring alternative protocols for sorafenib dose escalation, e.g., escalation to restore antitumour activity in patients whose disease progressed with reduced exposure, or regular monitoring of plasma concentrations and dose adjustment to maintain exposure over time [20, 24].

The present study assessed the use of scheduled intra-patient dose escalation to enhance response rates with sorafenib in patients with mRCC. We conclude that escalating the sorafenib dose from the standard 400 mg BID may have benefited individual patients able to tolerate this approach. However, the present study does not support this type of scheduled dose escalation for all patients with treatment-naïve mRCC. Alternative protocols for sorafenib dose escalation could be explored.

Acknowledgements

We thank all the patients, caregivers, and investigators who participated in this study. We also thank Jenny Handford and Jerry King from 7.4 Limited, who provided medical writing support funded by Bayer HealthCare Pharmaceuticals. The sponsor played a role in design and conduct of the study, collection, management, analysis, and interpretation of the data, and review and approval of the manuscript, and funded medical writing support for the preparation of this article.

Author Contributions

M.E. Gore and M. Kuczyk contributed to the study concept and design. A. Bearz, T. Demkow, M.E. Gore, R.J. Jones, C. Porta, and A. Ravaud acquired the data. M.E. Gore, M. Kuczyk, C. Porta, J. Shapiro, and U.P. Strauss analysed and interpreted the data. M.E. Gore, M. Kuczyk, and U.P. Strauss drafted the manuscript. T. Demkow, M.E. Gore, R.J. Jones, M. Kuczyk, C. Porta, A. Ravaud, J. Shapiro, and U.P. Strauss critically reviewed the manuscript for important intellectual content. J. Shapiro did the statistical analysis. R.J. Jones and M. Kuczyk provided administrative, technical, or material support.