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

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Take home message: This study tested the use of scheduled intra-patient dose escalation to enhance the clinical benefit of sorafenib in patients with renal cell carcinoma. Patients who tolerated this approach exhibited better outcomes than those who didn't, but relatively few patients could maintain doses higher than standard.

Patient summary: This study tested a strategy of increasing the daily dose of sorafenib according to a planned schedule for treatment of advanced kidney cancer, but allowing for reductions and delays in treatment to help manage side effects. We found that disease outcomes showed apparent improvement for those patients who could tolerate an increase in dose over time . However, many patients were unable to tolerate the higher doses due to side effects of the treatment. We conclude that this strategy may benefit some, but should not be recommended for all patients.

Trial registration: This clinical trial was registered with clinicaltrials.gov (NCT00618982).

Keywords: renal cell carcinoma, sorafenib, dose escalation, targeted therapy, tyrosine kinase inhibitor

Abstract

Background: Intra-patient dose escalation is a strategy which may enhance the clinical benefit of targeted anticancer agents in metastatic disease.

Objective: To assess the efficacy and safety of sorafenib dose escalation in patients with metastatic renal cell carcinoma (mRCC)

Design, setting, and participants: This non-randomized open-label Phase 2b study assessed sorafenib dose escalation in treatment-naïve patients with mRCC.

Intervention: Patients initially received the standard dose of 400 mg BID oral sorafenib. Two dose escalations in 200 mg BID increments were planned, each after 28 days at the prior level. Dose was reduced, interrupted, or dose escalation delayed to manage adverse events (AEs).

Outcome measurements and statistical analysis: The primary endpoint was objective tumour response rate (ORR) in the modified intent-to-treat (ITT) 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 and limitation: 83 patients received sorafenib. The dose received for the longest duration was 400 mg BID in 48.2% patients; 600 mg BID in 15.7% patients; 800 mg BID in 24.1% patients. ORR in the modified ITT population was 44.0% (n=8/18; 95% CI, 21.5–69.2); ORR in the ITT population was 17.9% (n=12/67; 95% CI, 9.6−29.2). Median PFS was 7.4 months (95% CI, 5.5–11.5) in the ITT population. The most common AEs of any grade were hand–foot skin reaction (66.3%) diarrhoea (63.9%), rash/desquamation (56.6%) and fatigue (54.2%).

Conclusions: Sorafenib demonstrated clinical benefit in treatment-naïve patients with mRCC. However, relatively few patients could sustain doses above 400 mg BID. There was evidence that where tolerated, escalation from the standard sorafenib dose may have provided 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.

1. Introduction

The advent of molecularly targeted agents brought welcome advances in the treatment of patients with metastatic renal cell carcinoma (mRCC). However, more effective approaches to this ultimately intractable 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/metastatic renal cell carcinoma (RCC) [1-6]. The pivotal TARGET trial demonstrated efficacy of sorafenib 400 mg twice daily (BID), which subsequently became the approved regimen [3-6].

In attempts to enhance clinical outcomes, doses of sorafenib higher than 400 mg BID have been investigated [7-9]. In a Phase 2 study of patients with mRCC, half of whom had received prior systemic therapy, the sorafenib dose was escalated at monthly intervals to 600 mg BID, then 800 mg BID [9]. Of the 44 patients evaluable for response, 70.5% received a dose escalation to 800 mg BID sorafenib; objective response rate (ORR) was 47.7%, and median PFS was 8.4 months [9]. These outcomes compared favourably with those of the TARGET study.

In light of these results, further investigation of sorafenib dose escalation was warranted. Here we report efficacy, safety and tolerability outcomes from an open-label Phase 2b study of planned sorafenib dose escalation in treatment-naïve patients with mRCC.

2. Patients and methods

2.1. Study design and patients

This was a non-randomized, open-label, uncontrolled, multicentre Phase 2b study (ClinicalTrials.gov NCT00618982). Eligible patients (aged ≥18 years) had histologically or cytologically confirmed metastatic clear cell RCC, with no prior systemic therapy for RCC; Eastern Cooperative Oncology Group performance status 0 or 1; intermediate or good prognosis according to the Memorial Sloan-Kettering Cancer Center scale; at least one measurable lesion by CT scan or MRI according to RECIST v1.0; life expectancy ≥12 weeks; prior total nephrectomy; and adequate bone marrow, liver, and renal function assessed within 7 days prior to study treatment. Prior palliative radiotherapy to metastatic lesions was permitted.

Exclusion criteria were: 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 [beta-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 cancer being evaluated in this trial [except cervical carcinoma *in situ*, treated basal cell carcinoma, superficial bladder tumours 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; biologic response modifiers, eg 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.

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

2.2. Treatment

Patients received initial treatment with 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 a further 28 days. However, if a patient developed any symptomatic AE ≥grade 3, except for nausea or vomiting, no dose escalation was allowed until the event resolved to at least grade 1. Treatment was maintained at the highest tolerated dose until disease progression, unacceptable toxicity, withdrawal of consent, investigator's decision, or study end. Dose delays or reductions to 400 mg daily or alternate days could be used to manage AEs. Specific criteria were defined for dose modification or delay due to dermatologic AEs, hypertension, hematologic AEs, and non-hematologic AEs (Supplementary Tables 1–5).

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

2.3. Assessments

Efficacy analyses were performed in the intention-to-treat (ITT) population, defined as all patients who received at least one sorafenib dose and had at least one valid efficacy evaluation post-baseline. For analysis of the primary endpoint, the modified ITT (mITT) population was defined as the subgroup of patients treated for at ≥6 months with ≥4 months at their highest tolerated sorafenib dose. Safety analyses were performed in all patients who received at least one sorafenib dose and for whom data were available after baseline.

The primary endpoint was ORR (complete or partial response) at 6 months in patients with ≥4 months of therapy at the highest tolerated dose. Secondary endpoints included PFS, disease control rate (DCR; complete or partial response, or stable disease), time to progression (TTP), safety and tolerability, and pharmacokinetics.

Tumour response and progression were assessed by central, independent, radiological review every 8 weeks using Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 [10]. 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. TTP was measured from the start of study medication to the first radiological or clinical progression. AEs were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0 [11]. Pharmacokinetic samples (6 mL) were collected on day 28 of the first completed cycle at each dose level at the following time points: pre-dose and 2, 4, 6, 8, 10 and 12 hours post-dose. Plasma levels of sorafenib and its metabolites (M2, M4, and M5) were measured to investigate the relationship between dose level and drug exposure.

2.4. Statistical analyses

No formal sample size calculation was required as this was an open-label study. The sample size was based on the width of the 95% confidence interval (CI) of the ORR, which would not exceed ±11% with a sample size of 80 patients.

3. Results

3.1. Patients

The first patient was treated on February, 04, 2008; the last visit of the last patient was January, 13, 2011. 89 patients were enrolled overall at 19 centres in France, UK, Germany, Italy, and Poland. Of these, 83 patients were treated with sorafenib and included in the safety population (Supplementary Figure 1).The ITT and mITT populations included 67 and 18 patients, respectively. Most of the ITT population excluded from the mITT analysis set discontinued sorafenib due to disease progression (Supplementary Table 6). Most patients in the safety population had more than one metastatic lesion (83.1%); the most frequent site of metastasis was lung (63.9% of patients) [Table 1].

Analysis of patients grouped by sorafenib dose received for the longest duration showed similar baseline demographics, although a higher proportion of patients had bone metastases in the 400 mg BID dose group compared with other groups (36.0%,16.7 %, and 15.0% in the 400, 600, and 800 mg BID dose groups, respectively). Mean time since diagnosis was 2.0, 0.7 and 2.3 years in the 400, 600 and 800 mg BID dose groups, respectively.

3.2. Treatment duration and doses received

Median treatment duration in the safety population was 225 days (range 7–1072 days) and mean (standard deviation) daily dose was 902 (364) mg/day. The median duration of follow-up in the safety population was 252 days (range 14–1071 days).

Of the 83 patients in the safety population, 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. Almost half of patients (n=40; 48.2%) received 400 mg BID for the longest duration (median duration [range], 29.5 days [7–855]), 20 patients

(24.1%) received 800 mg BID (177.5 days [56–956]), 13 patients (15.7%) received 600 mg BID (164 days [62–681]), 7 patients (8.4%) received 400 mg daily (434 days [122–764]), and 3 patients (3.6%) were on 400 mg every other day (332 days [136–675])

3.3. Efficacy

In the mITT population, all patients showed partial response (n=8/18) or stable disease (n=10/18). The primary efficacy endpoint, ORR, was 44.4% (95% CI 21.5–69.2%), and DCR was 100%. In the ITT population, ORR was 17.9% (n=12/67) [95% CI: 9.6–29.2%], and DCR was 86.6% (n=58/67) and (Table 2).. Tumour shrinkage assessed in independent central review was seen in 72%, 75%, and 85% of patients in the 400, 600, and 800 mg BID dose groups, respectively (Figure 2).

In the ITT population, median PFS was 7.4 months (95% CI: 6.0–11.7) overall (Table 2 and Figure 1). The percentage of patients who were progression-free was 62.3% at 6 months and 33.4% at one year. Median PFS was 3.7 (95% CI, 1.8–9.7 months) months, 7.4 (6.3–12.0) months, and 8.5 (5.6–14.9) months, respectively, for the groups that received 400 mg BID, 600 mg BID, and 800 mg BID for the longest period during the study. The findings for TTP were identical to those for PFS, because no deaths occurred before disease progression was observed.

3.4. Safety

All patients reported at least one treatment-emergent adverse event (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]. Most patients (90.4%) experienced 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]. Apart from hyponatraemia and elevated lipase (both n=2 [2.4%]), grade 4 events occurred in

individual patients only. Table 4 summarizes TEAEs by dose at first occurrence. Most patients (91.6%) experienced their first AE at a dose of 400 mg BID.

In the overall safety population, serious TEAEs were reported in 44 (53.0%) patients and most were single occurrences. The most common serious TEAEs, each occurring in 3 (3.6%) patients, were fatigue, rash/desquamation, and hyponatraemia.

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

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

3.5. Pharmacokinetics

The pharmacokinetics of sorafenib and its metabolites (M2, M4, and M5) were assessed after 28 days of continuous oral administration of 400 mg, 600 mg, or 800 mg BID. No increase in exposure (AUC or C_{max}) was observed with the increase in dose, indicating a lack of dose proportionality (Supplementary Table 7).

4. Discussion

In this open-label dose-escalation study, sorafenib showed clinical benefit in ORR, disease control rate, and PFS in treatment-naïve patients with mRCC.

In the ITT population, 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 (mPFS: 5.7–9.1 months; ORR, 5.2%–30.0%) [3,8,12-16]. These data do not therefore support dose escalation as a strategy for all patients in this setting. When ORR and PFS in different dose groups are compared, patients who tolerated higher doses of sorafenib (>400 mg BID) appear to have experienced enhanced clinical benefit compared with those receiving doses ≤400 mg BID. However, meaningful comparison between the dosage groups is limited because this small, non-randomized, uncontrolled study was not designed to explore this

The ORR for the mITT population (44.4%) compares favourably to other first-line sorafenib trials [3,8,12-16], and is similar to that in the Phase 2 dose-escalation study of Amato et al (47.7%) [9]. Although clinical trials cannot be directly compared, these observation suggest that mITT patients may have gained additional benefit from sorafenib dose escalation compared with the standard treatment. A number of patients were excluded from the mITT either because they received sorafenib for less than 6 months, or were not treated for 4 months at their maximum tolerated dose. Therefore patients who tolerated sorafenib well, and those whose disease responded better to sorafenib may be over-represented in the mITT population.

Outcomes in the ITT population appeared inferior to those reported by Amato and co-workers who followed a similar dose-escalation protocol. This may reflect the fact that sorafenib therapy and dose escalation were less well tolerated in this study. Of note, the numbers of grade 3/4 AEs in the Amato study were much lower, allowing a

greater proportion of patients to reach and potentially benefit from the 800 mg BID dose [9].

The pharmacokinetic analysis showed no apparent increase in sorafenib exposure at higher doses. However, patients were not randomized 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 [17]. 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 later than lower-dose samples, and sorafenib exposure declines over time [17,18].

No new or unexpected toxicities arose in our 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 [17]. Gastrointestinal disorders were the exception, most often starting with 600 or 800 mg BID. Again interpretation is difficult with respect to dose groups, but these findings 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 [18]. The small proportion of patients (24%) who could sustain the highest dose level and the need for frequent dose reductions and interruptions to manage adverse events, reflect 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, eg 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 [19,20].

5. Conclusions

Escalating sorafenib dose from the standard level of 400 mg BID may have benefited individual patients who were able to tolerate this approach. However, this study does not support a scheduled dose-escalation strategy of this type for all patients with treatment-naïve mRCC. Alternative protocols for sorafenib dose escalation could be explored.

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Tables and figures

Table 1. Baseline demographic and clinical characteristics

	Safety population	ITT population			
	Overall (n=83)	**Overall (n=67)**	**400 mg BID[a] (n=25)**	**600 mg BID[a] (n=12)**	**800 mg BID[a] (n=20)**
Median (range) age, years	61 (33-80)	62 (33-80)	64 (44-80)	59 (33-78	57 (39-72)
Male, n (%)	54 (65.1)	44 (65.7)	15 (60.0)	9 (75.0)	15 (75.0)
ECOG PS, n (%)					
0	49 (59.0)	40 (59.7)	14 (56.0)	7 (58.3)	13 (65.0)
1	34 (41.0)	27 (40.3)	11 (44.0)	5 (41.7)	7 (35.0)
Disease stage, n (%)					
III	1 (1.2)	1 (1.5)	0	0	0
IV	82 (98.8)	66 (98.5)	25 (100.0)	12 (100.0)	20 (100.0)
Clinical/radiological status					
Stable disease	15 (18.1)	12 (17.9)	4 (16.0)	2 (16.7)	2 (10.0)
Progressive disease	68 (81.9)	55 (82.1)	21 (84.0)	10 (83.3)	18 (90.0)
Mean (SD) time since initial diagnosis[b], years	2.1 (3.1)	2.0 (3.1)	2.0 (3.1)	0.7 (0.7)	2.3 (3.0)
Number of metastatic sites, n (%)					
1	14 (16.9)	0	0	0	0
≥2	69 (83.1)	67 (100)	25 (100.0)	12 (100.0)	20 (100.0)
Metastatic sites, n (%)					
Lung	53 (63.9)	51 (76.1)	20 (80.0)	11 (91.7)	14 (70.0)
Lymph nodes	33 (39.8)	33 (49.3)	10 (40.0)	7 (58.3)	11 (55.0)
Liver	25 (30.1)	25 (37.3)	8 (32.0)	4 (33.3)	9 (45.0)
Bone	16 (19.3)	16 (23.9)	9 (36.0)	2 (16.7)	3 (15.0)

Prior therapy for RCC, n (%)					
Surgery	83 (100.0)	67 (100.0)	25 (100.0)	12 (100.0)	20 (100.0)
Radiotherapy	12 (14.5)	10 (14.9)	4 (16.0)	3 (25.0)	1 (5.0)
Systemic anticancer therapy	3 (3.6)	2 (3.0)	1 (4.0)	0 (0.0)	0 (0.0)

BID, twice daily; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PS, performance status; RCC, renal cell carcinoma; SD, standard deviation

[a]Dose taken for the longest time period while in the study; ten patients treated at doses <400 mg BID are not included because of small sample sizes

[b]These data were unavailable for one patient in each of the overall safety population, the overall ITT population, and the 400 mg BID group

Table 2a. Tumour response and progression-free survival in the mITT population

	Overall (n=18)	**400 mg QOD[a] (n=2)**	**400 mg once-daily[a] (n=5)**	**400 mg BID[a] (n=1)**	**600 mg BID[a] (n=2)**	**800 mg BID[a] (n=8)**
Partial response, n (%)	8 (44.4)	0	2 (40.0)	1 (100.0)	1 (50.0)	4 (50.0)
Stable disease, n (%)	10 (55.6)	2 (100.0)	3 (60.0)	0	1 (50.0)	4 (50.0)
Progressive disease, n (%)	0	0	0	0	0	0
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)
Disease control rate‡, % (95% CI)	100.0 (81.5−100.0)	100 (15.8−100.0)	100 (47.8−100.0)	100 (2.5−100.0)	100 (15.8−100.0)	100 (63.1−100.0)

BID, twice daily; CI, confidence internal; ITT, intention-to-treat; mITT, modified ITT; ND, not determined; PFS, progression-free survival; QOD, every other day
No complete responses were recorded
[a]dose taken for the longest time period while in the study

Table 2b. Tumour response and progression-free survival in the ITT population

	Overall (n=67)	**400 mg QOD[a] (n=3)**	**400 mg once-daily[a] (n=7)**	**400 mg BID[a] (n=25)**	**600 mg BID[a] (n=12)**	**800 mg BID[a] (n=20)**
Partial response, n (%)	12 (17.9)	0	2 (28.6)	1 (4.0)	2 (16.7)	7 (35.0)
Stable disease, n (%)	46 (68.7)	3 (100)	5 (71.4)	15 (60.0)	10 (83.3)	13 (65.0)
Progressive disease, n (%)	9 (13.4)	0	0	9 (36.0)	0	0
Response rate[b], % (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)
Disease control rate[c], % (95% CI)	86.6 (76−93.7)	100 (29.2–100)	100 (59.0–100)	64.0 (42.5−82.0)	100 (73.5−100.0)	100 (83.2−100.0)
Median (95% CI) PFS, months	7.4 (5.5–11.5)	ND[d]	ND[d]	3.7 (1.8–9.7)	7.4 (6.3–12.0)	8.5 (5.6–14.9)
Progression-free at 6 months, %	55.3	ND[d]	ND[d]	49.1	75.0	58.6
Progression-free at 12 months, %	34.6	ND[d]	ND[d]	24.6	22.2	39.1

BID, twice daily; CI, confidence internal; ITT, intention-to-treat; mITT, modified ITT; ND, not determined; PFS, progression-free survival; QOD, every other day
No complete responses were recorded
[a]dose taken for the longest time period while in the study
[b]Response rate defined as complete response + partial response
[c]Disease control rate defined as complete response + partial response + stable disease
[d]These data were not determined due to the small sample sizes for these subgroups

Table 3. Incidences of treatment-emergent adverse events 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), n (%)

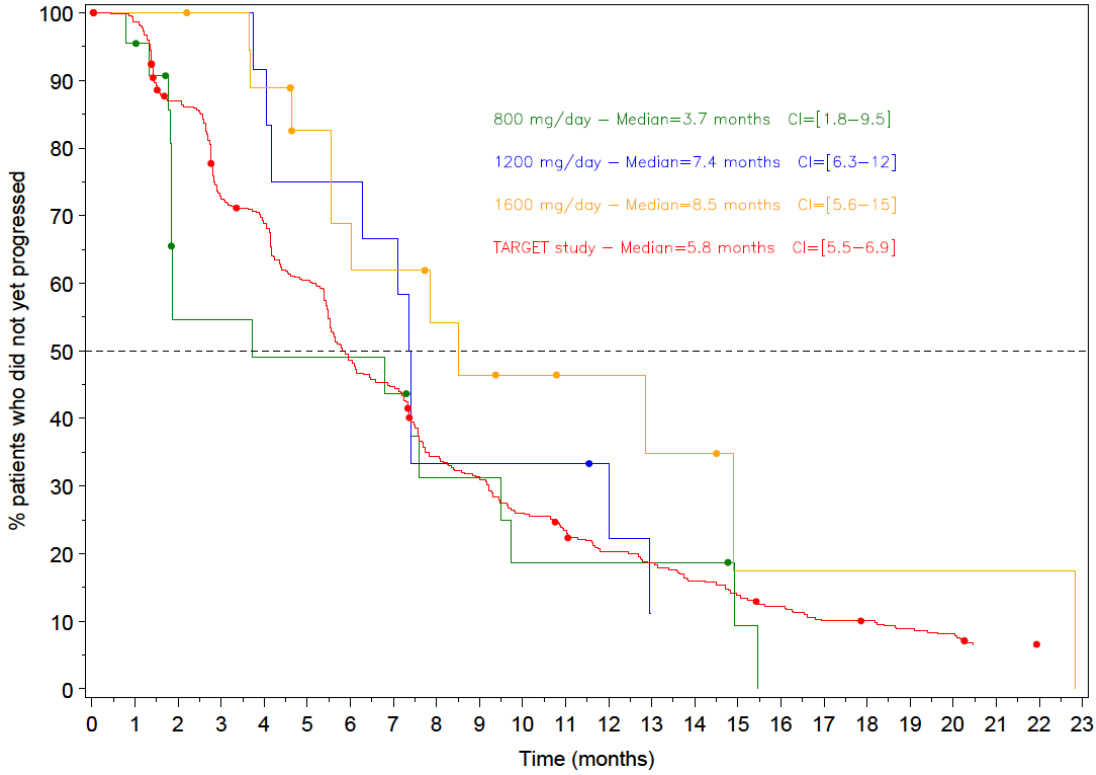
Adverse event	Any grade	Grade 3	Grade 4
Any event	83 (100.0%)	61 (73.5%)	13 (15.7%)
Hand–foot skin reaction	55 (66.3%)	21 (25.3%)	0
Diarrhoea	53 (63.9%)	10 (12%)	1 (1.2%)
Rash/desquamation	47 (56.6%)	11 (13.3%)	0
Fatigue	45 (54.2%)	13 (15.7%)	1 (1.2%)
Hypertension	40 (48.2%)	5 (6.0%)	0
Alopecia	36 (43.4%)	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
Dyspnoea (shortness of breath)	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%)	3 (3.6%)	0
Alanine aminotransferase	7 (8.4%)	5 (6%)	0
Hyponatraemia	5 (6%)	3 (3.6%)	2 (2.4%)

Table 4. Incidences of treatment-emergent adverse events (any grade, occurring in >10% of patients in any category) by dose at first occurrence (safety population), n (%)

Adverse event	400 mg QOD 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 (10.0)	5 (13.2)	76 (91.6)	0	1 (2.5)
Hypertension	2 (20.0)	4 (10.5)	29 (34.9)	2 (3.8)	2 (5.0)
Fatigue	2 (20.0)	2 (5.3)	29 (34.9)	4 (7.7)	5 (12.5)
Weight loss	0	0	5 (6.0)	2 (3.8)	7 (17.5)
Alopecia	1 (10.0)	5 (13.2)	16 (19.3)	9 (17.3)	5 (12.5)
Dry skin	1 (10.0)	1 (2.6)	13 (15.7)	3 (5.8)	5 (12.5)
Hand–foot skin reaction	0	3 (7.9)	43 (51.8)	5 (9.6)	4 (10.0)
Pruritus	0	2 (5.3)	10 (12.0)	2 (3.8)	0
Rash/desquamation	1 (10.0)	1 (2.6)	38 (45.8)	5 (9.6)	2 (5.0)
Anorexia	1 (10.0)	0	6 (7.2)	8 (15.4)	6 (15.0)
Diarrhoea	1 (10.0)	3 (7.9)	21 (25.3)	19 (36.5)	9 (22.5)
Oral mucositis (functional/symptomatic)	1 (10.0)	2 (5.3)	19 (22.9)	4 (7.7)	1 (2.5)
Nausea	2 (20.0)	2 (5.3)	10 (12.0)	3 (5.8)	5 (12.5)
Vomiting	0	1 (2.6)	8 (9.6)	2 (3.8)	5 (12.5)
Hypocalcaemia	0	0	1 (1.2)	0	5 (12.5)
Hypophosphataemia	0	1 (2.6)	13 (15.7)	3 (5.8)	0

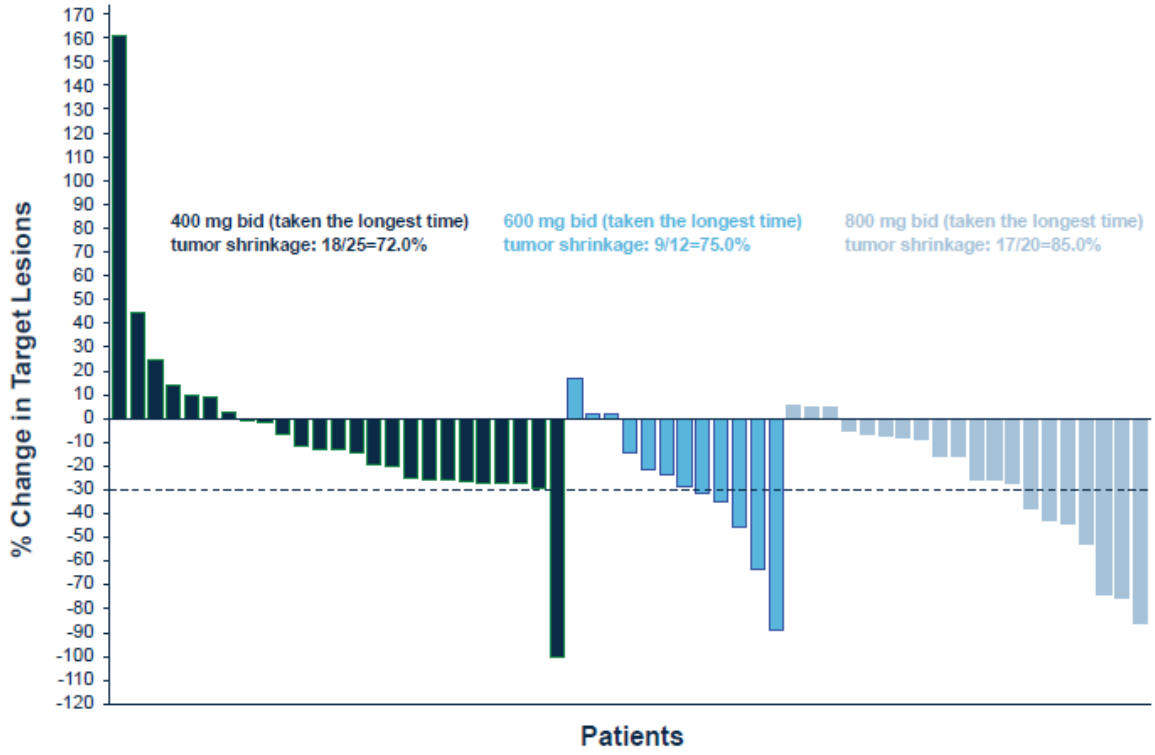
BID, twice daily; NOS, not otherwise specified; OD, once daily; QOD, every other day.

Figure 1. Kaplan-Meier graph showing progression-free survival by independent central assessment according to the dose received for the longest duration in the study (ITT population). The PFS curve from the phase 3 trial of sorafenib for treatment of mRCC (TARGET) is shown for comparison [4].



CI, confidence interval; BID, twice daily; ITT, intent-to treat; PFS, progression-free survival; mRCC, metastatic renal cell carcinoma.

Figure 2. Maximum tumour shrinkage (% change from baseline in target lesions by independent assessment) according to the dose received for the longest duration in the study (ITT population)



Dotted line represents the threshold for response using RECIST v1.0.

Supplementary materials

Supplementary Table 1.Predefined dose modification levels for treatment with sorafenib

Dose level -2	400 mg every-other-day
Dose level -1	400 mg once-daily
Dose level 1	400 mg twice-daily
Dose level 2	600 mg twice-daily
Dose level 3	800 mg twice-daily

Supplementary Table 2. Criteria for sorafenib dose delay and dose modification due to skin toxicities

Toxicity grade		**During a course of therapy**	**Dose for next cycle[a]**
Grade 1		Maintain dose level	Maintain dose level
Grade 2[b]	1st appearance	Interrupt until resolved to grade 0/1	Maintain dose level
	2nd appearance	Interrupt until resolved to grade 0/1	Decrease by one dose level
	3rd appearance	Interrupt until resolved to grade 0/1	Decrease by two dose levels
	4th appearance	Discontinue treatment permanently	Discontinue treatment permanently
Grade 3	1st appearance	Interrupt until resolved to grade 0/1	Decrease by one dose level[c]
	2nd appearance	Interrupt until resolved to grade 0/1	Decrease by two dose levels
	3rd appearance	Discontinue treatment permanently	Discontinue treatment permanently

[a]**One cycle = 28 days**

[b]The investigator has the option of continuing therapy through a grade 2 skin toxicity with the exception of the following: hand–foot skin reaction, erythema multiforme; ulceration; wound complication. The investigator must follow the above criteria for subjects presenting with any of these skin toxicities.

[c]For subjects who require a dose reduction for grade 3 rash or hand–foot skin reaction, the dose may be increased to the starting dose after one full cycle (28 days) of therapy has been administered at the reduced dose without the appearance of rash or hand foot syndrome ≥ grade 1.

Supplementary Table 3. Management of treatment-emergent hypertension

Grade of event (NCI-CTCAE v3)	Management/next dose
Grade 1 asymptomatic and transient	Consider increased BP monitoring
Grade 2 asymptomatic and diastolic BP < 110 mm Hg	Begin anti-hypertensive therapy and continue sorafenib
Grade 2 symptomatic/ persistent *or* diastolic BP ≥ 110 mm Hg *or* Grade 3	Sorafenib should be stopped[a] until symptoms resolve and diastolic BP returns to ≤100 mm Hg. Treat subject with anti-hypertensives and when sorafenib is restarted, reduce by 1 dose level[b] (refer to table 2) If diastolic BP not controlled to ≤100 mm Hg on therapy, reduce sorafenib by another dose level and monitor BP closely[c]
Grade 4 life-threatening	Discontinue protocol therapy

BP, blood pressure; NIC-CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events.

Please note that specific criteria are not completely identical to NCI-CTCAE v3.

[a]Subjects requiring a delay of >28 days should go off protocol therapy.

[b]May be able to resume full dose later.

[c]Subjects requiring >2 dose reductions should go off protocol therapy.

Supplementary Table 4. Criteria for dose delay and dose modification due to heematologic AEs

Grade	Dose delay	Dose modification
Grade 0–2	Treat on time	No Change
Grade 3	Treat on time	Decrease one dose level[b]
Grade 4	Delay[a] until ≤grade 2	Decrease one dose level[b]

[a]If no recovery after 28 day delay, treatment will be discontinued unless subject is deriving clinical benefit

[b]If more than two dose reductions are required, treatment will be discontinued

Supplementary Table 5. Criteria for dose delay and dose modification due to non-haematologic AEs (except skin toxicity)[a]

Grade	Dose delay	Dose modification
Grade 0–2	Treat on time	No change
Grade 3	Delay[b] until ≤grade 2	Decrease one dose level [c]
Grade 4	Discontinue protocol therapy	Discontinue protocol therapy

[a]Also excludes nausea/vomiting that has not been pre medicated, and diarrhoea

[b]If no recovery after 28 day delay, treatment will be discontinued unless subject is deriving clinical benefit

[c]If no If more than 2 dose reductions are required, treatment will be discontinued

Supplementary Table 6. Reasons for permanent discontinuation of sorafenib, for patients in the ITT population who did not qualify for the mITT population by last dose received, n(%)

	Overall	**400 mg QOD**	**400 mg once daily**	**400 mg BID**	**600 mg BID**	**800 mg BID**
Adverse event	14 (28.6)	0	3 (6.1)	6 (12.2)	4 (8.2)	1 (2)
Disease progression, recurrence or relapse	32 (65.3)	1 (2)	4 (8.2)	10 (20.4)	4 (8.2)	9 (18.4)
Other[a]	3 (6)	0	1 (2)	2 (4)	0	0

BID, twice daily; ITT, intention-to-treat; mITT, modified ITT; QOD, every other day
[a]Other reasons for discontinuation were recorded as one case each of: clinical endpoint reached; completed all planned treatments; and investigator decision, not protocol driven.

Supplementary Table 7. Pharmacokinetic parameters for sorafenib and its metabolites (M2, M4, and M5) after 28 days of twice daily dosing with sorafenib 400 mg, 600 mg or 800 mg BID (all patients valid for pharmacokinetics)

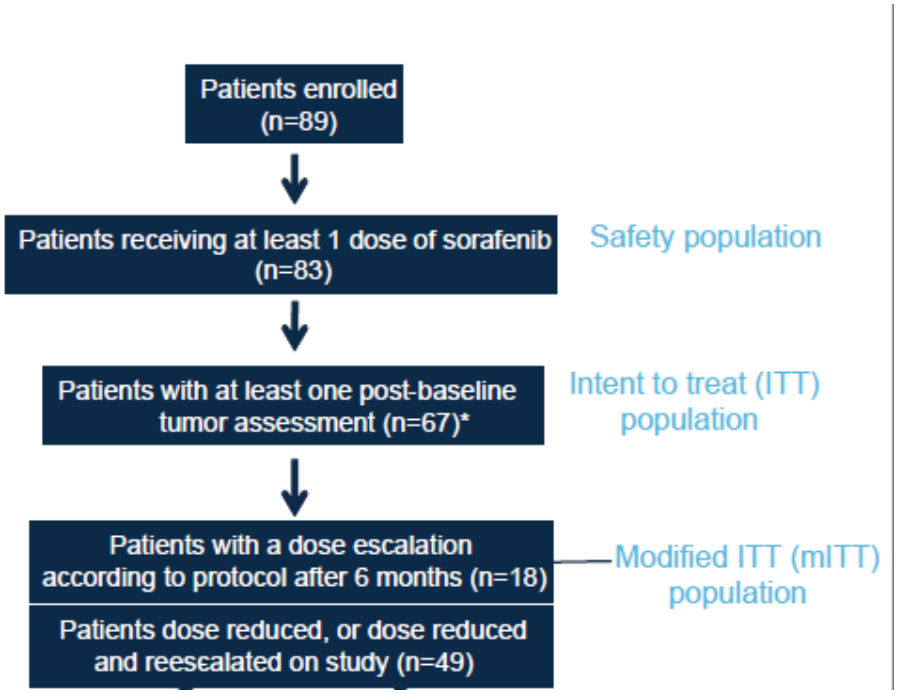
Parameter	400 mg BID			600 mg BID			800 mg BID		
	n	Geometric mean[a]	%CV[a]	n	Geometric mean[a]	%CV[a]	n	Geometric mean[a]	%CV[a]
Sorafenib									
$AUC_{(0–8)ss}$ (mg·h/L)	40	40.61	39.5	30	41.84	43.5	28	36.19	45.1
$AUC_{(0–10)ss}$ (mg·h/L)	40	49.98	39.2	30	51.24	43.7	26	43.83	47.8
$AUC_{(0–12)ss}$ (mg·h/L)	32	57.18	39.1	23	57.56	46.1	19	46.98	51.9
C_{max} (mg/L)	40	7.53	38.0	31	7.62	39.3	28	6.64	42.1
t_{max} (h)	40	2.0	(0–12.0)	31	2.0	(0–12.0)	28	2.0	(0–12.0)
Metabolite M2									
$AUC_{(0–8)ss}$ (mg·h/L)	40	7.11	75.4	30	8.39	82.7	28	6.99	89.4
$AUC_{(0–10)ss}$ (mg·h/L)	40	8.80	74.3	30	10.36	82.1	27	8.23	87.2
$AUC_{(0–12)ss}$ (mg·h/L)	32	9.58	78.2	23	11.24	75.9	20	8.41	94.6
C_{max} (mg/L)	40	1.31	80.8	31	1.51	81.4	28	1.30	88.5
t_{max} (h)	40	2.0	(0–10.3)	31	2.0	(0–12.0)	28	1.0	(0–12.0)
Metabolite M4									
$AUC_{(0–8)ss}$ (mg·h/L)	40	2.5	81.4	30	2.44	87.0	28	1.88	80.8
$AUC_{(0–10)ss}$ (mg·h/L)	40	3.1	80.8	30	3.04	86.5	27	2.22	77.2
$AUC_{(0–12)ss}$ (mg·h/L)	32	3.33	77.2	23	3.25	77.8	20	2.39	83.5
C_{max} (mg/L)	40	0.48	90.1	31	0.47	88.0	28	0.36	82.8
t_{max} (h)	40	0	(0–10.1)	31	2.0	(0–12.0)	28	2.0	(0–12.0)
Metabolite M5									
$AUC_{(0–8)ss}$ (mg·h/L)	40	2.13	141.3	30	2.77	140.8	28	2.65	147.9
$AUC_{(0–10)ss}$ (mg·h/L)	40	2.65	139.5	30	3.44	141.5	27	3.03	137.0

Parameter	400 mg BID			600 mg BID			800 mg BID		
	n	Geometric mean[a]	%CV[a]	n	Geometric mean[a]	%CV[a]	n	Geometric mean[a]	%CV[a]
$AUC_{(0–12)ss}$ (mg·h/L)	31	3.03	117.6	23	3.55	135.5	20	3.19	162.2
C_{max} (mg/L)	40	0.40	144.6	31	0.52	136.6	28	0.49	145.0
t_{max} (h)	40	0	(0–12.0)	31	2.0	(0–12.0)	28	0	(0–12.0)

[a]Except t_{max}, for which median and range are presented.

$AUC_{(0–X)ss}$, area under the curve from time 0 to X hours post-dose at steady state; BID, twice daily; C_{max}, maximum plasma concentration; CV, coefficient of variation; ss, steady state; t_{max}, time to maximum plasma concentration.

Supplementary Figure 1. Patient flow



* Efficacy evaluated every two cycles.