European Journal of Cancer 108 (2019) 69–77

Available online at www.sciencedirect.com

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Clinical Trial

The efficacy and safety of sunitinib given on an individualised schedule as first-line therapy for metastatic renal cell carcinoma: A phase 2 clinical trial

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Received 29 August 2018; received in revised form 24 November 2018; accepted 9 December 2018
Available online 14 January 2019

KEYWORDS
Kidney neoplasm;
Sunitinib;

Abstract ***Background:*** Sunitinib is administered on a rigid schedule that may not be optimal for all patients. We hypothesised that toxicity-driven dose and schedule changes would optimise drug exposure and outcome for each patient.

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https://doi.org/10.1016/j.ejca.2018.12.006

Medicine individualised; Drug dosing biomarker

Materials and methods: In a phase 2 trial, 117 patients with metastatic clear cell renal cell cancer were started on sunitinib 50 mg/day with the aim to treat for 28 days. Treatment breaks were reduced to 7 days. Sunitinib dose and the number of days on therapy were individualised based on toxicity aiming for ≤ grade II toxicity with dose escalation in patients with minimal toxicity. The null hypothesis for the primary end-point was a progression-free survival (PFS) of 8.5 months based on a study with similar eligibility criteria.
Results: The null hypothesis was rejected ($p < 0.001$) with a median PFS of 12.5 months (95% confidence interval [CI]: 9.6–16.5). The median overall survival was 38.5 months (95% CI: 28.3-not reached). The objective response rate (46.1%) and stable disease rate (38.5%) translated into a clinical benefit for 84.6% of patients with no decline in quality of life scores during therapy. Fewer patients were dose reduced (26.5% vs. 50%) or discontinued due to toxicity (7.7 vs. 18–20%) compared to standard sunitinib dosing, and 20 (18.4%) patients were dose escalated to 62.5 mg (12) and 75 mg (8) with a wide individual variation in the optimal dose and treatment duration.
Conclusions: : Individualised sunitinib therapy is feasible, safe and an effective method to manage toxicity with one of the best efficacy seen for oral vascular endothelial growth factor inhibitors in metastatic renal cell carcinoma.
Clinicaltrials.gov identifier: NCT01499121.

1. Introduction

Sunitinib is a first-line therapy for metastatic renal cell carcinoma (mRCC), with a recommended starting dose and schedule of 50 mg daily for 28 days followed by a 14-day break (4/2 schedule) with dose reductions for toxicity to 37.5 mg and 25 mg on the same schedule. Higher sunitinib blood levels are associated with a longer progression-free survival (PFS), overall survival (OS) and a higher objective response rate (ORR) [1], and blood levels reach a steady state after 10–14 days [2]. This is consistent with our microbubble ultrasound data [3] for patients responding to sunitinib that suggest most of the benefit from sunitinib may be achieved well before day 28, that a shorter duration of therapy may be better than a premature dose reduction, and that the treatment break should be shorter to avoid tumour progression [4,5]. We reported an inferior ORR, PFS and OS in patients experiencing minimal toxicity on the standard 50 mg 4/2 schedule compared with patients who developed toxicity and required dose/schedule modifications [3]. Other studies, including retrospective analysis of three randomised trials [6–8], have confirmed this observation [9–13]. It was hypothesised that the poor outcome in patients who tolerate the 50-mg standard 4/2 schedule without toxicity was because of underdosing and that toxicity-driven dose and schedule changes would optimise drug exposure for each patient and improve outcomes.

2. Materials and methods

2.1. Patient population

The eligibility criteria for the present study were similar to the EFFECT trial [7] for which median PFS (8.5 months) on the 4/2 arm was used as the historical control to power our study. These included age 18 years or older, untreated locally recurrent or metastatic RCC (clear cell or with a component of clear cell histology), measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, Karnofsky performance status ≥ 80% and adequate organ function. Exclusion criteria included brain metastases or spinal cord compression, significant cardiovascular or pulmonary events within 6 months and uncontrolled hypertension.

2.2. Study design and treatment

In this multicenter open-label phase 2 trial, patients were started on sunitinib 50 mg/day with the aim to treat for 28 days. Treatment breaks were reduced from the standard 14 days to 7 days. Sunitinib dose and the number of days on therapy were individualised based on toxicity aiming for ≤ grade II toxicity (oral mucositis, diarrhoea, hand-foot syndrome, neutropenia, thrombocytopenia and fatigue) as outlined in Fig. 1 to establish the optimal dose and schedule for each patient (optimal dosing). Hypertension responding to antihypertensives was not used to individualise therapy as this could limit optimal dosing. Other less common toxicities and biochemical toxicities were managed according to standard sunitinib guidelines. If grade II toxicity developed before day 28, drug was held for 7 days (d). Therapy was then continued on a 50 mg dose with the number of days on therapy individualised based on toxicity. The dose was only reduced to 37.5 mg and then 25 mg if patients did not tolerate a 50 mg or 37.5 mg dose, respectively, for at least 7 days. Patients with ≤ grade I toxicity after 28 days on therapy were dose escalated to 62.5 mg and then 75 mg on a schedule of 14 days on/7 days off. Patients were contacted by telephone weekly and came for clinic visits every 2 weeks until

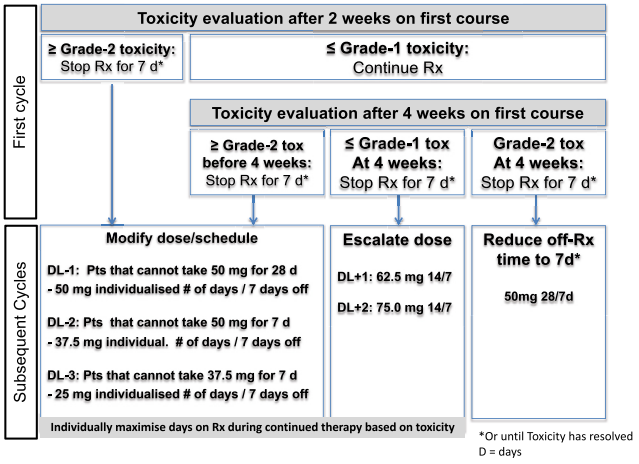

Fig. 1. Dose/schedule allocation during the first and subsequent treatment cycles to establish the optimal dose and schedule (optimal dosing) for each patient. Dose and schedule changes were individualised by the treating oncologist based on toxicity aiming for ≤ grade II toxicity (oral mucositis, diarrhoea, hand-foot syndrome, neutropenia, thrombocytopenia and fatigue). Other less common toxicities and biochemical toxicity were managed according to the standard prescribing information for sunitinib. d = days; DL = dose level; Pts, patients; Rx = treatment. *Or until toxicity has resolved.

optimal dosing was established. Patients were then contacted by telephone regarding toxicity and had blood tests before each course of therapy and came for clinic visits every 2 months. A patient diary was used to monitor compliance.

2.3. Study end-points and assessment

The primary end-point was PFS. Secondary end-points included safety, ORR, OS, patient-reported outcomes and sunitinib pharmacokinetics.

Radiographic response assessment by computed tomography was performed every 8 weeks until progression. Blood sampling was carried out for plasma sunitinib and its metabolite (SU012662) concentrations as described in the online supplement. Patient-reported outcome data were collected at baseline and every 8 weeks using the Functional Assessment of Cancer Therapy General Scale (FACT-G) [14] and the Kidney Symptom Index Disease-Related Symptoms questionnaire (FKSI-DRS) [15].

The study was approved by Health Canada and conducted in accordance with the Guidelines of Good Clinical Practice. The protocol was approved by local ethics boards at each institution, and patients signed an informed consent. An independent data monitoring committee assessed safety data every 6 months.

2.4. Statistical analysis

Based on the standard dosing arm (4/2) of the EFFECT trial [7], that had similar eligibility criteria, we assumed a median PFS of 8.5 months (95% confidence interval [CI] 6.9–11.1) in patients receiving standard sunitinib dosing. Based on retrospective data [3,10,12], we assumed that individualised dosing would improve the median PFS to 14 months. Thus, setting the null hypothesis as median PFS of 8.5 months vs. the alternate hypothesis of a median PFS of 14 months, with a two-sided alpha = 0.05, in a single-arm non-parametric survival test, we would have over 90% power to detect this difference with 99 patients on study. Accounting for a 10% loss to follow-up, we aimed to accrue 110 patients. If the true median PFS of patients treated with individualised dosing was 12 or 13 months, this trial design with a sample size of 99 patients would still have over 67% and 81% power, respectively, to detect this difference.

Analyses of ORR, PFS and OS were based on intention to treat. Safety was analysed for all patients who received at least one dose of sunitinib. Kaplan–Meier analysis was used for time to event analysis. Median and log–log 95% confidence interval was reported. The time of all follow-up was calculated from the first treatment to the last follow-up or death. ORR was defined as the proportion of patients with best response of complete response (CR) or partial response (PR) according to RECIST 1.1 criteria. Confirmed responses were those that persisted on repeat imaging at 8 weeks. ORR and 95% CI were calculated using the exact method and compared between the International mRCC Database Consortium (IMDC) groups by Fisher's exact test.

Safety was assessed by history, physical examination and blood tests and graded according to the Common Terminology Criteria for Adverse Events, version 3·0.

Patient-reported outcomes were analysed using mixed-effects modelling, with the intrapatient correlation accounted for using a compound symmetric correlation structure.

Dose intensity at the optimal dose and schedule was calculated as the actual daily dose of sunitinib received during a 6-week period divided by the recommended 50 mg/day dose given on the standard 4/2 schedule as previously reported [16]. The analysis of plasma sunitinib and SU012662 is described in the online supplement. The cutoff date for all analyses was July 24, 2017. Statistical analyses were performed with SAS, version 9.4. Sample size calculations were performed with the SWOG statistical tool for one arm non-parametric survival.

3. Results

From July 9 2012 to February 6, 2015, 181 patients were assessed with 64 deemed ineligible and 117 enrolled in 12 cancer centres (Supplementary Fig. S1). All 117 patients started therapy, but nine came off study before confirmatory imaging due to global deterioration (1), clinical progression (1), non-compliance (2), Guillain-Barré syndrome (1) and toxicity (grade III–IV liver toxicity [2],

grade IV thrombosis [1], multiple grade II toxicities [1]). Of 108 patients, where optimal dosing was established, 7 are still on therapy. The remaining 101 patients came off therapy due to RECIST progression (84), death unrelated to sunitinib (1), clinical progression (1), patient wishes/non-compliance (5), global deterioration (1) physician decision (2), cholecystitis (2), and toxicity (grade III fatigue [2], congestive heart failure [1], grade III neutropenia [1], grade II diarrhoea and subsequent colitis [1]).

Patient characteristics (Table 1) are comparable to the EFFECT trial, but more patients in our study had Karnofsky performance score ≥ 90 and no patients had a score of 70.

Table 2 shows the dose and schedule when therapy was discontinued for the 108 patients where optimal dosing was established. The median time to optimal dosing was 4 months (range 1.8–13.2) with some patients adding days on therapy or dose escalating late during therapy. In 20 patients (18.5%), dose was escalated to 62.5 mg (12) and 75 mg (8), with a dose intensity of 1.3 and 1.5, respectively. Of the 36 patients ever escalated to 62.5 mg, 12 dose reduced to 50 mg, 6 stayed on 62.5 mg and 18 escalated to 75 mg. Of the 18 patients ever dose escalated to 75 mg, 8 stayed on 75 mg, 10 went back to 62.5 mg and 4 of these went back to 50 mg. In 50 patients (46.3%), a 50 mg dose was continued but for less than 28 days (dose intensity 0.9), thus avoiding a reduction to 37.5 mg as per standard dosing criteria. In 21 patients (19.4%) dose was reduced to 37.5 mg (dose intensity 0.8), and in 10 patients (9.3%), dose was reduced to 25 mg (dose intensity 0.5). Six patients received continuous dosing at 25 mg (2) and 37.5 mg (4) rather than dose escalation to the next higher dose level as per protocol due to patient/physician decision. An extra 7-day treatment break was allowed on 13 treatment cycles due to patients' travel and family events. Supplementary Table S1 shows the large interindividual differences in optimal dose and treatment duration vs. ORR. See details on therapy given after sunitinib was discontinued in online Supplement.

Table 1
Patient characteristics for 117 patients compared with the EFFECT study.

Characteristics	Present study N = 117 No (%)	EFFECT study N = 146 No (%)	P value
Age (years): median (range)	60 (42–84)	61 (35–84)	–
Sex			0.355
Men	87 (74.4)	101 (69.2)	
Women	30 (25.6)	45 (30.8)	
IMDC risk group			0.324
Favourable	37 (31.6)	37 (25.3)	
Intermediate	67 (57.3)	87 (59.6)	
Poor	13 (11.1)	22 (15.1)	
MSKCC risk group			0.759
Favourable	37 (31.6)	43 (29)	
Intermediate	73 (62.4)	91 (62)	
Poor	7 (6)	12 (8)	
Number of metastatic sites			0.918
1	26 (22.2)	33 (22.6)	
≥2	91 (77)	112 (76.7)[a]	
2	32 (27.4)	–	
3	37 (31.6)	–	
4	17 (14.5)	–	
5	3 (2.6)	–	
6	2 (1.7)	–	
Sites of metastases			–
Bone	26 (22.2)	34 (23.3)	
Liver	28 (23.9)	24 (16.4)	
Lung	90 (76.9)	104 (71.2)	
Lymph nodes	59 (50.4)	–	
Local recurrence only	4 (3.4)	–	
Brain	0	0	
Nephrectomy	104 (88.9)	117 (80.1)	0.054
Previous radiation	16 (13.7)	19 (13.0)	0.875
Karnofsky performance score			
≥90	98 (83.8)	105 (71.9)	0.026
80	19 (16.2)	37 (25.4)	
70	0 (0)	4 (2.7)	

IMDC = International mRCC Database Consortium. MSKCC = Memorial Sloan-Kettering Cancer Centre
Full data not available for the EFFECT study.
[a] Missing data for 1 patient.

Table 2
Dose and schedule distribution for 108 pts on optimised dosing.

Sunitinib dose (mg)	Schedule (days on/off)	Patients currently on or came off therapy on this dose and schedule	Median dose intensity
75	18/7	1	20 pts (18.5%)
75	14/7	4	dose escalated
75	10/7	1	Median dose
75	7/7	2	intensity (DI)
62.5	16/7	2	1.5 at 75 mg
62.5	14/7	4	1.3 at 62.5 mg
62.5	12/7	1	
62.5	10/7	1	
62.5	7/7	4	
50	28/7	6	7 pts (6.5%) on
50	28/14	1	for 28 days, DI = 1
50	25/7	1	In 50 pts (46.3%)
50	24/7	2	50 mg dose
50	16/7	2	maintained with
50	14/7	22	fewer days on Rx.
50	13/7	1	Would have been
50	12/7	1	dose reduced by
50	9/7	2	standard criteria
50	7/7	19	DI = 0.9
37.5	Continuous	4	21 pts (19.4%) dose
37.5	21/7	1	reduced to 37.5 mg
37.5	14/7	5	DI = 0.8
37.5	11/7	2	
37.5	9/7	1	
37.5	7/7	8	
25	Continuous	2	10 pts (9.3%)
25	14/7	4	reduced to 25 mg
25	7/7	4	DI = 0.5

Pts, patients.

3.1. Efficacy

The PFS was calculated from the date of starting sunitinib for 117 patients with 85 events (RECIST progression or death) observed. Others were censored on the date off-treatment or the last date of the last cycle. The median time of all follow-up from the first treatment to the last follow-up or death was 28.8 months (range 2.1–57). The median PFS was 12.5 months (95% CI: 9.6–16.5) (Fig. 2 panel a). There was a statistically significant difference ($p < 0.001$ and $p = 0.01$) in the median PFS based on IMDC and Memorial Sloan-Kettering Cancer Centre (MSKCC) risk groups, respectively; favourable group 22.0 months (95% CI 17.7–28.7) and 22.8 months (95% CI 19.3–28.7), intermediate group 9.9 months (95% CI 7.8–13.8) and 9.2 months (95% CI 7.4–12.5), poor group 4.8 months (95% CI 1.8–7.5) and 13.8 months (95% CI 5.1 –not reached, only 7 patients), intermediate and poor groups combined 9.6 months (95% CI: 7.4–12.5) and 9.2 months (95% CI: 7.4–12.5).

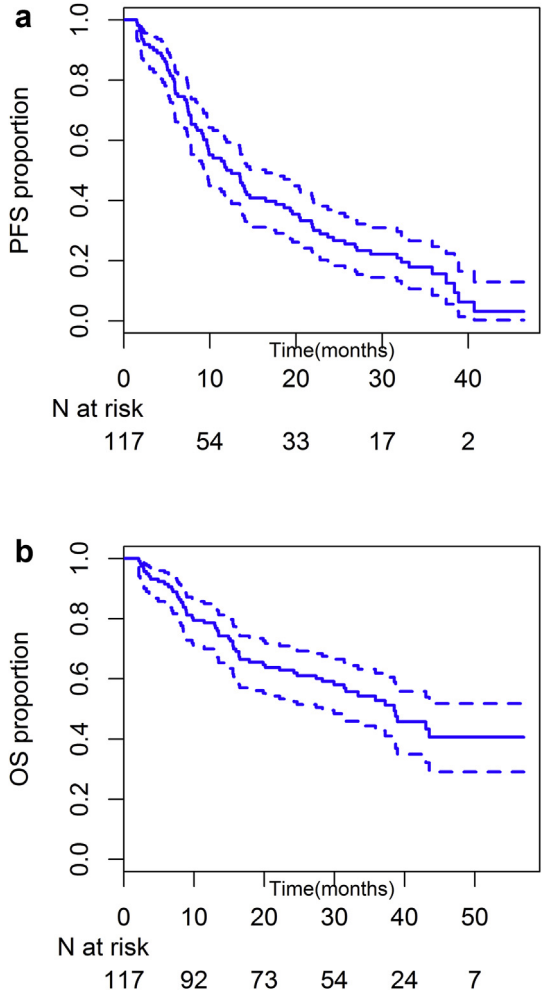

Fig. 2. (a) Kaplan–Meier estimates of progression-free survival. (b) Kaplan–Meier estimates of overall survival. N at risk = number of patients at risk; OS = overall survivals; PFS = progression-free survival.

The OS was calculated from the start of sunitinib therapy in 117 patients with 58 deaths observed and others censored on the last follow-up date (Fig. 2 panel b). The estimated median OS was 38.5 months (95% CI: 28.3-not reached). There was a difference ($p < 0.001$) in median OS based on IMDC and MSKCC risk groups respectively; favourable group not reached for both, intermediate group 35.9 months (95% CI 24.2–43.5) and 31.6 months (95% CI 17.9–43.0), poor group 6.4 months (95% CI 3.2–9.7) and 11.4 months (95% CI 2.5–16.5, only 7 patients), intermediate and poor groups combined 28.3 months (95% CI: 15.6–38.5) and 28.3 months (95% CI: 16.4–38.5).

For 117 patients who started sunitinib, 3 (2.6%) had a CR, 51 (43.6%) a PR and 45 (38.5%) stable disease (SD) for an ORR of 46.1% (95% CI 36.9–55.6) and a clinical benefit rate of 84.6%. The median duration of ORR and SD was 12.8 months (range 3.2–44.6) and 7,4 months (range 2.02–36.3), respectively. Progressing disease (PD) was the best response in 9 patients (7.7%), and 9 patients (7.7%) were not evaluated. There was a difference ($p = 0.006$) in ORR based on IMDC risk groups; favourable group 56.8% (95% CI 39.5–72.9), intermediate group 47.8% (95% CI 35.4–60.3), poor group 7.7% (95% CI 0.2–36.0). The ORR for the intermediate and poor groups was 41.3% (95% CI: 30.4–52.8).

Fig. 3 shows waterfall plots for dose vs. ORR and dose intensity vs. ORR in 108 dose optimised patients. There was no association (by log-rank test) between ORR and dose (<50, 50 mg, > 50 mg, $p = 0.48$), dose intensity (>0.87 vs < 0.87, $p = 0.73$) or duration of therapy (>14, 14 or <14 days, $P = 0.175$).

For all 117 patients, there was no association between PFS and OS and dose given (<50, 50 mg, > 50 mg, $p = 0.11$ and 0.25, respectively), duration of therapy (>14, 14 or <14 days, $P = 0.464$ and 0.21, respectively) or dose intensity (>0.87 vs < 0.87, $p = 0.10$ and 0.2, respectively).

The results of the pharmacokinetic analyses are described in the online supplement.

There were no significant changes (supplementary Fig. S4) during therapy in the mean quality of life scores for the FACT-G and the FKSI-DRS ($p = 0.58$ and 0.10, respectively).

3.2. Safety

The dose and schedule for each patient was individualised aiming for grade II toxicity (Fig. 1). Most patients settled on a dose and schedule that resulted in noticeable toxicity, between grade I and grade II, that they could accept long term. Supplementary Table S3 shows the most common ≥ grade II toxicities that led to dose/schedule changes in 108 patients on optimised dosing. Supplementary Table S4 shows the main treatment-related toxicities in all 117 patients. There were no toxic deaths.

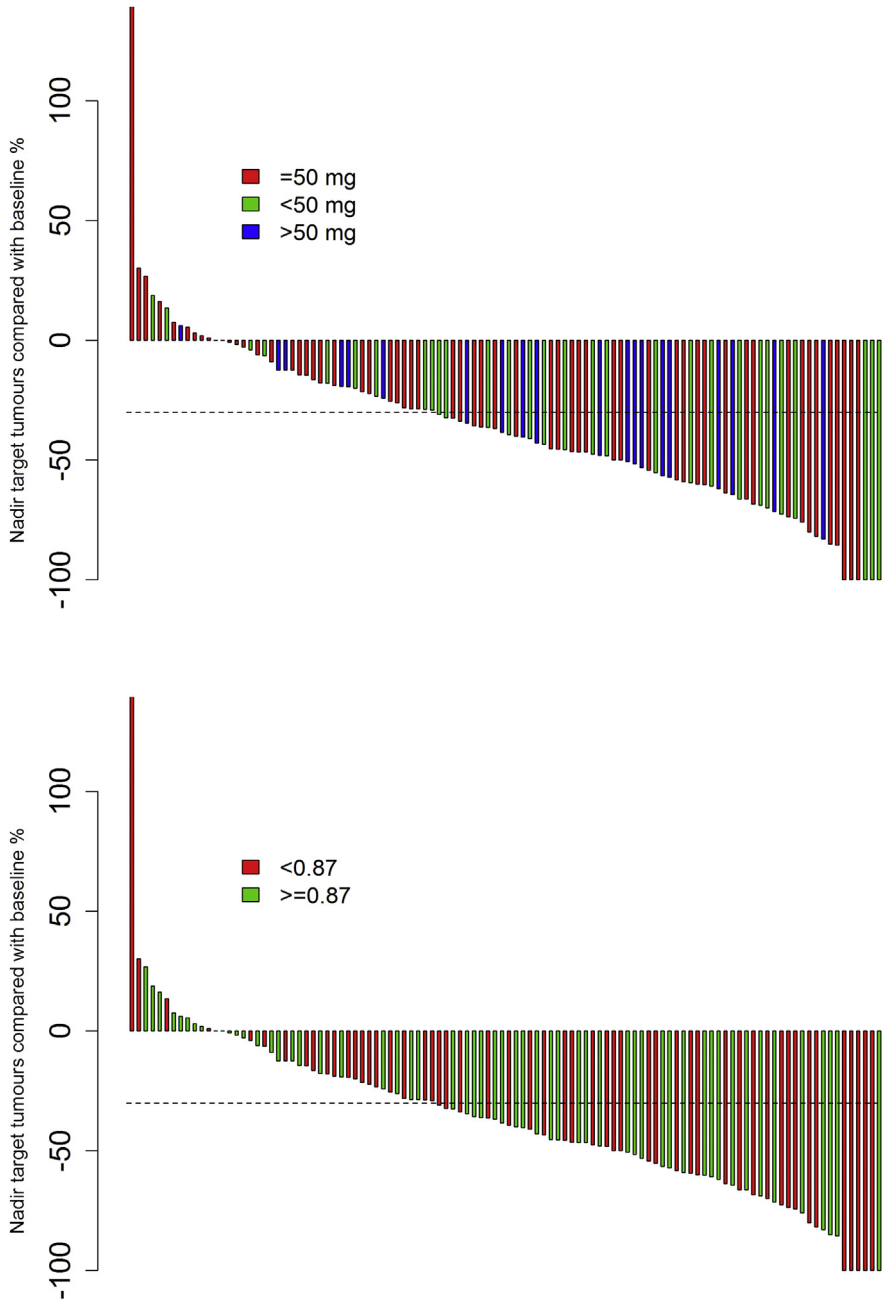

Fig. 3. a) Dose vs. response in 108 patients with optimised dose/schedule; =50 = patients on 50 mg dose; <50 = patients on less than 50 mg dose; >50 = patients on more than 50 mg dose. (b) Dose intensity vs. response in 108 patients with optimised dose/schedule; <87 = patients receiving less than the median dose intensity of 0.87; > 87 = patients receiving more than the median dose intensity of 0.87.

4. Discussion

Individualised sunitinib therapy is feasible and safe in a multicenter setting and an effective method to manage toxicity with no decline in quality of life scores during therapy. The median PFS on the standard 4/2 arm in the comparator study [7] was 8.5 months (95% CI 6.9–11.1). With 117 patients analysed (99 required), the null hypothesis of PFS being 8.5 months can be rejected at the <0.001 significance level with the lower limit of our CI (9.6 months) > 8.5 months. While no direct comparison can be made between trials, our efficacy data compare favourably to contemporary data for sunitinib, axitinib and pazopanib [7,8,17] and to recent data for IMDC intermediate and poor risk patients [18,19] (Supplementary Tables S5 and S6). Dose reductions were required in 31/117 patients (26.5%), and therapy was discontinued due to toxicity in 9/117 (7.7%). In previous sunitinib trials, 50% of patients required dose reduction [6] and 18–20% discontinued due to

toxicity [6,8]. There was a large interindividual variability in the optimal dose and schedule for each patient and no association between ORR, PFS or OS vs. dose given or vs. dose intensity. One dose, dose intensity or duration of therapy does not fit all.

The concept of individualised therapy challenges the use of rigid dosing schedules for oral targeted drugs. Individualising the number of days on therapy before changing the dose allows more detailed dosing. A 2 weeks on/1 week off (2/1) schedule has been found to be active and less toxic than the 4/2 schedule [20,21]. Based on the dose/schedule distribution (Table 2) in our study, the 2/1 schedule was optimal in only 31 (35.2%) of 88 patients that were not dose escalated. Replacing one rigid schedule (4/2) with another (2/1) would have led to underdosing in 64.8% of patients who could have either taken drug for more than 14 days or where dose was reduced rather than taking drug for less than 14 days. This does not take into account the 20 patients (18%) that could be dose escalated. Intermittent sunitinib dosing based on response has also been found to be feasible and active [22].

Our data may have implications for the dosing of other oral vascular endothelial growth factor (VEGF) inhibitors given alone or in combination with immunotherapy [23]. Oral VEGF inhibitors will be used for all patients that are not cured by immunotherapy [19]. As for sunitinib [1], there is an association between higher drug levels and better outcome for pazopanib [24] and axitinib [25], and higher drug levels may impact the activity of adjuvant therapy [26]. Patients tolerating continuous dosing of oral VEGF inhibitors with minimum toxicity may be underdosed both in the metastatic and adjuvant setting [27,28]. Consistent with our scheduling method, dose escalation based on toxicity is the standard of care for axitinib and individualising axitinib dose and duration based on toxicity with planned breaks off therapy has been found feasible and active [29].

This study has several limitations. It is single arm and with a relatively small sample size. Our study entered significantly more patients with a better performance status and numerically more patients with better IMDC and MSKCC criteria (Table 1). This could impact the observed results vs. the EFFECT trial. A prospective randomised trial is required to conclusively establish the value of individualised therapy. An ongoing phase II trial (NCT02689167) is comparing three different schedules for sunitinib.

5. Conclusions

Individualised sunitinib therapy is safe and an effective method to manage toxicity with one of the best efficacy seen for oral VEGF inhibitors in mRCC. There was no decline in quality of life scores during therapy. A similar dosing strategy may improve outcomes and tolerability for other oral VEGF-targeted drugs.

Conflict of interest statement

Georg A Bjarnason received honoraria from Pfizer, Novartis, Bristol-Myers Squibb, Eisai and Ipsen; research funding from Pfizer and Novartis and travel funding from Pfizer and Novartis and is a consultant to Pfizer, Novartis, Bristol-Myers Squibb, Eisai and Ipsen. Jennifer J Knox is a consultant to Merck and received research funding from AstraZeneca and Pfizer. Christian K Kollmannsberger received honoraria from Pfizer, Novartis and Bristol-Myers Squibb and travel funding from Pfizer, Novartis and is a consultant to Pfizer, Novartis, Seattle Genetics, Bristol-Myers Squibb and Astellas Pharma . Denis Soulieres received honoraria from Merck, Novartis, Pfizer, AstraZeneca, Roche, Ipsen and Bristol-Myers Squibb and research funding from Novartis, Pfizer, Merck, Roche, Bristol-Myers Squibb and Lilly and is a consultant to Merck, Pfizer and Ipsen. D. Scott Ernst is a consultant to Bristol-Myers Squibb, Roche, Novartis, Merck and AstraZeneca. Pawel Zalewski is a consultant to Novartis, Pfizer, Roche and Bristol-Myers Squibb. Christina M Canil is a consultant to Eisai, Merck, Novartis, Bristol-Myers Squibb, Janssen, AstraZeneca, Roche, Sanofi and Pfizer and received research funding from Hoffman−La Roche, AstraZeneca, Janssen, Eisai and Merck and travel funding from Pfizer, Sanofi and Amgen. Eric Winquist received honoraria from Merck, Bayer and Eisai and research funding from Sanofi, Exelixis, Oncogenex, Roche, AstraZeneca, Medivation and Eisai. Sebastien J Hotte received honoraria from Astellas, Janssen, AstraZeneca, Bayer and research funding: Agensys, AstraZeneca, Bayer, Roche, Merck, Clovis Oncology, Corvus Pharmaceuticals, Bristol-Myers Squibb and Abbvie/Genentech and is a consultant to Janssen, Astellas, Bristol-Myers Squibb, Bayer, Pfizer, AstraZeneca, Merck and Roche. Scott A North received honoraria from Janssen-Ortho, Astellas, Novartis, Pfizer, Sanofi and research funding from Roche, Sanofi, Novartis, Astellas, Janssen and AstraZeneca and is a consultant Janssen, Astellas, Novartis, Sanofi, Roche, Merck, AstraZeneca and Roche. Daniel YC Heng is a consultant to Pfizer, Novartis, Bristol-Myers Squibb, Astellas and received research funding Pfizer, Novartis, Exelixis and Bristol-Myers Squib. Robyn J Macfarlane received honoraria from Merck, Bristol-Myers Squibb and Novartis. Anil Kapoor received honoraria from Pfizer, Novartis, Bristol-Myers Squibb and Ipsen and research funding from Novartis, Pfizer and Bristol-Myers Squibb. Aaron R Hansen received honoraria from Merck, AstraZeneca Pfizer, Novartis, Merck, Serono Boehringer Ingelheim, Bristol-Myers Squibb and research funding from Karyopharm Therapeutics,

Merck, Bristol-Myers Squibb, Boehringer Ingelheim, Novartis and Glaxo. Bernhard J Eigl received honoraria from Pfizer and Janssen and travel funding from Janssen and AstraZeneca; is a consultant to Roche, AstraZeneca and Merck and a member of the Speakers' Bureau of Merck. Piotr Czaykowski received research funding from Pfizer. Ben Boyd is employed to Syneos Health. Naveen S Basappa received honoraria from Pfizer, Bristol-Myers Squibb, Merck, AstraZeneca, Janssen and Astellas and travel funding from Janssen and is a consultant to Pfizer, Bristol-Myers Squibb, AstraZeneca, Janssen, Astellas, Ipsen and Bayer. The other authors have none to declare.

Funding and support

Pfizer Inc. funded this study as an investigator-initiated grant to Dr. Bjarnason. The trial was managed and all data were collected and analysed by Ozmosis Research Inc. (Toronto, Ontario). Pfizer Inc. funded this study and provided free drug as required. The study design was proposed by Dr. Bjarnason and the coauthors and approved by Pfizer. Pfizer had no role in data collection or data analysis but had an opportunity to comment on the final manuscript.

Acknowledgements

The authors thank Pfizer Inc. for funding this study and the many Pfizer staff in Canada and the US who supported this concept with special thanks to Dr. Susan W. Pitman Lowenthal. They thank all the staff at Ozmosis Research Inc. who managed the study with special thanks to Pamela Degendorfer, Jessie Miller, Daniel Farago and Ben Boyd. They also thank the patients and their families and all the investigators and their local clinical trials teams. There was no professional writing assistance used for this manuscript.

The following are the investigators who entered patients on this study: Dr. G. Bjarnason, Dr. Jennifer Knox, Dr. Naveen Basappa, Dr. Christian Kollmannsberger, Dr. Scott Ernst, Dr. Denis Soulieres, Dr. P. Zalewski, Dr. Sebastien Hotte, Dr. Eric Winquist, Dr. Christina Canil, Dr. Daniel Heng, Dr. Bernie Eigl, Dr. Piotr Czaykowski, Dr. Scott North, Dr. Peter Venner, Dr. Robyn Macfarlane, Dr. Anil Kapoor, Dr. Ian Tannock, Dr. Aaron Hansen, Dr. Atul Sharma, Dr. Joel. Gingerich, Dr. Greg Lo, Dr. Henry Conter, Dr. Kylea Potvin, Dr. Martin Neil Reaume, Dr. Carmel Jacobs, Dr. Lori Wood, Dr. Dean Ruether, Dr. Nimira Alimohamed, Dr. Anthony Joshua.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.12.006.

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