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Sunitinib administered on 2/1 schedule in patients with metastatic renal cell carcinoma: the RAINBOW analysis

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Background: First-line sunitinib is recommended in metastatic renal cell carcinoma (mRCC), but it is frequently associated with relevant toxicities and subsequent dose reductions. Alternative schedules, such as 2-week-on treatment and 1-week-off (2/1 schedule), might improve tolerability. We evaluated the safety and outcomes of this schedule in a large multicenter analysis.

Patients and methods: Retrospective, multicenter analysis of mRCC patients treated with first-line sunitinib on a 2/1 schedule. Data of 249 patients were reviewed: 208 cases who started sunitinib on the 4/2 schedule (full dosage: 188/208, 90.4%) and thereafter switched to the 2/1 schedule for toxicity (group 4/2→2/1) and 41 patients who started first-line sunitinib with the 2/1 schedule because of suboptimal clinical conditions (group 2/1). A total of 211 consecutive patients treated with the 4/2 schedule in another institution served as external controls. Safety was the primary end point. Treatment duration (TD), progression-free survival (PFS) and overall survival (OS) were also analyzed.

Results: In group 4/2→2/1, the overall incidence of grade ≥3 toxicities was significantly reduced (from 45.7% to 8.2%, $P < 0.001$) after the switch to 2/1 schedule. This advantage was maintained also in the 106/188 cases (56.4%) who maintained the full dosage. Fatigue, hypertension, hand–foot syndrome and thrombocytopenia were less frequent. The incidence of grade ≥3 adverse events in the negatively selected group 2/1 (only 73.2% starting at full dose) was 26.8%, similar to what observed in the external control group (29.4%). Median TD was 28.2 months in the 4/2→2/1 group (total time spent with both schedules), 7.8 months in the 2/1 group and 9.7 months in external controls. Median PFS was 30.2, 10.4 and 9.7 months, respectively. Median OS was not reached, 23.2 and 27.8 months, respectively.

Conclusions: mRCC patients who moved to a modified 2/1 schedule of sunitinib experience an improved safety profile compared with that observed during the initial 4/2 schedule.

Key words: mRCC, sunitinib, treatment schedule, toxicity

introduction

Sunitinib is a tyrosine kinase inhibitor for the vascular endothelial growth factor receptor and the platelet-derived growth factor receptor which has shown to increase progression-free survival (PFS), compared with interferon-α, in patients with metastatic renal cell carcinoma (mRCC) [1–3]. On this basis, sunitinib currently represents one of the standards of care for first-line therapy in patients with favorable-intermediate risk mRCC [4, 5].

The standard dosing schedule for sunitinib is 50 mg once/daily for 4 consecutive weeks on treatment followed by 2-week-off (4/2 schedule) [6, 7]. The 2-week-off period has been recommended to allow patients to recover from treatment-related adverse events (TRAEs) such as fatigue, hypertension and hematological toxicities, which frequently appear after the first 2 weeks of treatment and tend to worsen in the following days [6]. Adverse events often lead to dose reductions or interruptions,

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with a negative impact on patient quality of life and outcome given the established relationship between dose intensity and efficacy [8, 9].

Some alternative schedules have been tested in order to improve the safety profile of sunitinib and increase dose intensity [10]. A randomized phase II trial evaluated sunitinib on a continuous 37.5 mg daily dosing and failed to demonstrate any advantage compared with the standard schedule [11]. Other recent studies have evaluated a modified 2-week-on and 1-week-off schedule (2/1 schedule) demonstrating improved tolerability and clinical outcomes [12–16]. However, these data are based on single-center experiences with a limited number of patients; therefore larger studies are required to further evaluate the efficacy and safety of the 2/1 schedule.

In our large multicenter, retrospective analysis, we evaluated the safety and efficacy of the 2/1 schedule of sunitinib, widely used in the Italian daily practice, after some preliminary data on this schedule had been reported. A group of mRCC patients treated with the standard 4/2 schedule at the Institute Gustave Roussy (Villejuif, France), an European referral center for treatment of mRCC, was used as external control.

patients and methods

patients and setting

We retrospectively reviewed data from patients with mRCC and adequate information on treatment compliance, response and follow-up, who were consecutively treated with first-line sunitinib on a modified schedule of 2-week on and 1-week off (2/1 schedule) at 24 Italian Oncology Centers (both local and referral Centers for treatment of mRCC).

For each patient, the following data were extracted by the database of each Center and analyzed: nephrectomy status, histology, initial Eastern Cooperative Oncology Group (ECOG) performance status and prognostic score based on the International Metastatic renal cell carcinoma Database Consortium (IMDC) criteria [17], sites of metastases and initial dose of sunitinib with dose changes and treatment-related toxicities. Patients were required to have regular evaluations for toxicity and treatment compliance every 6 weeks and radiological evaluations by computed tomography or magnetic resonance every 12 ± 1 weeks as required by Italian guidelines.

The same data were extracted from mRCC patients treated with the standard 4/2 schedule at Gustave Roussy in order to get adequate control from an external referral center of recognized experience in the treatment of mRCC.

The local Ethical Committees approved the study protocol.

study end points

The primary end point of this study was safety. The change in incidence of TRAEs between the two treatment periods was evaluated in patients switching from the 4/2 to the 2/1 schedule. The overall and the incidence of grade ≥3 TRAEs was estimated in each group of patients included in the analysis. TRAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event version 3.0 or 4.0 by experienced medical oncologists.

In addition, the following outcomes were considered in an exploratory fashion: treatment duration (TD), progression-free survival (PFS) and overall survival (OS). TD was defined as the time from the initiation of sunitinib to discontinuation or death. The TDs under the 4/2 schedule (i.e. from initiation to discontinuation of sunitinib at 4/2 schedule) and under the 2/1 schedule (i.e. from initiation to discontinuation of sunitinib at 2/1 schedule) were also considered for patients who modified the initial schedule. PFS was defined as the time from the initiation of sunitinib to the documented disease progression or death, and OS was defined as time from the initiation of sunitinib to death from any cause.

data analysis

Descriptive statistics were used to summarize the data. The change of the incidence of grade ≥3 toxicities was tested among patients who switched from 4/2 to 2/1 schedule by the Mc Nemar test. In patients who switched from the 4/2 to the 2/1 schedule due to treatment-related toxicities, the dosage of sunitinib at the schedule switch was recorded (50 mg versus others). An explorative analysis of survival adjusted according to the IMDC criteria was also carried out.

Median TD, PFS and OS were estimated according to the Kaplan–Meier method. Interquartile range (IQR) of TD and confidence intervals (CIs) of median survival times were calculated according to the Brookmeyer–Crowley log–log method. Adjusted estimates of the survivor functions were based on the corrected group prognosis method, applied on the results of a Cox proportional hazards model stratified by Heng criteria. A P value <0.05 was considered significant. All analyses were carried out by SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

results

patient populations

A total of 249 patients were treated with first-line sunitinib from November 2005 to August 2013 and were included in the study: 208 patients switched from the 4/2 to the 2/1 schedule (4/2→2/1 group)—of whom 188 (90.4%) started on the standard dosage—and 41 started sunitinib with the 2/1 schedule (2/1 group)—of whom 30 (73.2%) started on the standard dosage—due to non-optimal general conditions according to the local treating oncologist. A total of 211 patients received the standard 4/2 schedule regimen and served as controls (4/2 group).

Baseline patients' characteristics are reported in Table 1. Some differences were observed: patients in the 4/2→2/1 group had overall more favorable characteristics compared with the other two groups in term of histology (clear cell in 94.7% of patients, versus 87.8% in the 2/1 group and 86.7% in the control group; $P = 0.01$), burden of disease and prognostic classification according to IMDC criteria (favorable risk in 42.3%, 24.4% and 34.1% of patients, respectively; $P = 0.05$). Although statistical significance was not reached likely due to the much smaller number of patients compared with the other groups, patients in the 2/1 group had a worse ECOG performance status (≥1: 26.9% in the 4/2→2/1 group, 41.5% in the 2/1 group and 26% in the control group, respectively; $P = 0.15$) and IMDC score, and presented more brain metastases at baseline (3.8%, 9.8% and 3.8%, respectively; $P = 0.20$).

safety

In 4/2→2/1 group, the most frequent reasons for changing schedule were: fatigue (23.5%), mucositis (16.2%), diarrhea (11.5%) and hand–foot syndrome (10.3%). In this group, 106 of the 188 patients who started sunitinib at 50 mg (56.4%) maintained the full dose of sunitinib after switching.

The incidence of severe adverse events (grade ≥3) was significantly reduced after the switch to the 2/1 schedule, compared with the incidence reported during the initial 4/2 schedule

Table 1. Baseline characteristics of patients

Characteristics	Group 4:2→2:1 ($N = 208$)	Group 2:1 ($N = 41$)	External control group ($N = 211$)	P value
Age (years)				
Median (range)	62 (25–82)	61 (32–82)	59 (28–86)	0.13
Gender, no. (%)				
Male	149 (71.6)	26 (63.4)	164 (77.7)	0.11
Female	59 (28.4)	15 (36.6)	47 (22.3)	
ECOG PS, no. (%)				
0	152 (73.1)	24 (58.5)	156 (73.9)	0.15
1	52 (25.0)	15 (36.6)	53 (25.1)	
2 or more	4 (1.9)	2 (4.9)	2 (0.9)	
Histotype, no. (%)				
Clear cell	197 (94.7)	36 (87.8)	183 (86.7)	0.01
Papillary	7 (3.4)	3 (7.3)	22 (10.4)	
Chromophobe	2 (1.0)	2 (4.9)	5 (2.4)	
Unknown or missing	2 (1.0)	–	1 (0.5)	
Heng prognostic classification, no. (%)				
Favorable risk	88 (42.3)	10 (24.4)	72 (34.1)	0.05
Intermediate risk	109 (52.4)	27 (65.8)	128 (60.7)	
Poor risk	11 (5.3)	4 (9.8)	11 (5.2)	
Lung involvement, no. (%)				
No	84 (40.4)	14 (34.1)	73 (34.6)	0.43
Yes	124 (59.6)	27 (65.9)	138 (65.4)	
Bone involvement, no. (%)				
No	163 (78.4)	30 (73.2)	157 (74.4)	0.57
Yes	45 (21.6)	11 (26.8)	54 (25.6)	
Liver involvement, no. (%)				
No	176 (84.6)	30 (73.2)	170 (80.6)	0.19
Yes	32 (15.4)	11 (26.8)	41 (19.4)	
CNS involvement, no. (%)				
No	200 (96.2)	37 (90.2)	203 (96.2)	0.20
Yes	8 (3.8)	4 (9.8)	8 (3.8)	

ECOG PS, Eastern Cooperative Oncology Group Performance Status; CNS, central nervous system.

(maximum toxicity grade ≥3: 45.7% in the 4/2 phase versus 8.2% in the 2/1 phase, $P < 0.001$) (Table 2A). The incidence of some grade 3–4 toxicities commonly associated with sunitinib such as fatigue (10.1% in the 4/2 phase versus 0% in the 2/1 phase; $P < 0.001$), hypertension (9.1% versus 2.4%; $P = 0.007$), hand–foot syndrome (10.1% versus 3.4%; $P = 0.003$) and thrombocytopenia (7.7% versus 0.5%; $P < 0.001$) was also reduced. The maximum toxicity grade (≥3) was also significantly reduced in the 106 patients of the 4/2→2/1 group who maintained the full dose of sunitinib (50 mg) after switching (41.5% versus 6.6%; $P < 0.001$; supplementary Table S1, available at *Annals of Oncology* online).

The incidence of the adverse events in the 2/1 group, in which 30 of 41 cases (73.2%) started sunitinib at full dosage, is reported in Table 2B. The incidence of grade ≥3 toxicities was 26.8%, with an overall incidence of adverse events of 80.5% and diarrhea as the most frequent severe adverse event (12.2%).

The incidence of the adverse events in the 4/2 group is reported in Table 2C. Overall, TRAEs were reported in 59.2% of patients, with 29.4% experiencing grade 3–4 events. The most common severe adverse events were hand–foot syndrome and hypothyroidism (7.1%).

treatment duration and survival

In the 4/2→2/1 group, the median overall TD was 28.2 months (IQR: 14.2–70.8). In the same group, median TD with the initial schedule 4/2 was 4.3 months (IQR: 2.0–12.0) and 19.7 months (IQR: 7.3–NR) with the following 2/1 schedule. In the 2/1 and 4/2 groups, median TD was 7.8 months (IQR: 5.8–22.4) and 9.7 months (IQR: 5.3–16.7), respectively.

Median PFS was 30.2 months (95% CI 23.2–47.1) in the 4/2→2/1 group, 10.4 months (95% CI 7.7–23.0) in the 2/1 group and 9.7 months (95% CI 8.9–11.7) in the 4/2 group (Figure 1).

The median OS was not reached in the 4/2→2/1 group, with a 36-month survival rate of 72.7% (95% CI 63.3–79.9), 23.2 months (95% CI 10.6–NE) in the 2/1 group (survival rate 32.0%, 95% CI 11.6% to 54.7%) and 27.8 months (95% CI 23.1–35.8) in the 4/2 group (survival rate 42.3%, 95% CI 34.5% to 50.0%) (Figure 2). After the adjustment for IMDC criteria, 36-month PFS and OS rates were 45.5% (95% CI 37.8% to 52.9%), 16.9% (95% CI 12.7% to 21.6%) and 6.9% (95% CI 6.4% to 7.4%); and 74.1% (95% CI 61.1% to 83.3%), 39.4% (95% CI 24.4% to 54.0%) and 39.5% (95% CI 33.2% to 45.7%), in the 4/2–>2/1, 2/1 and control group, respectively (supplementary Figures S1 and S2, available at *Annals of Oncology* online).

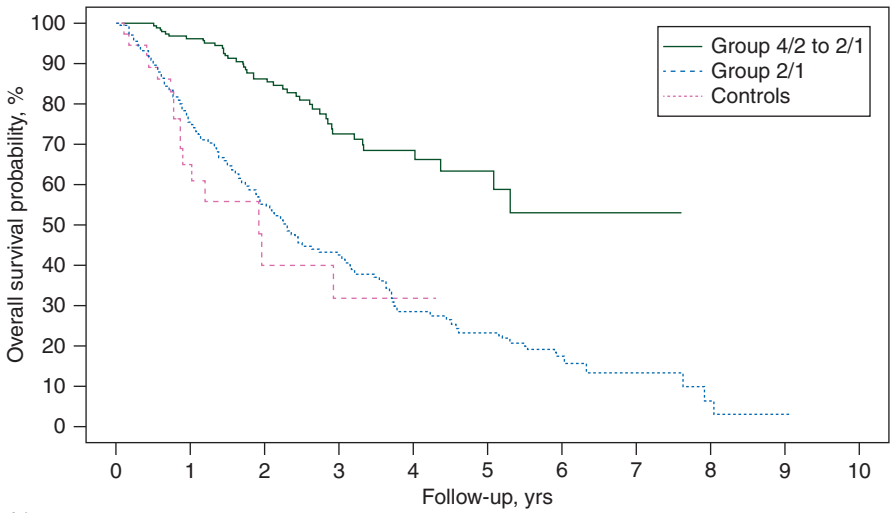
Table 2. Incidence of NCI-CTC TRAEs in (A) patients of the group 4:2→2:1, according to treatment schedule; (B) patients of the group 2:1 ($N = 41$); (C) patients of the external control group ($N = 211$)

A)					
Adverse event	Initial schedule 4/2 period ($N = 208$)		Subsequent schedule 2/1 period ($N = 208$)		*P* value*
	Any grade	Grade 3–4	Any grade	Grade 3–4	
Diarrhoea, no. (%)	87 (41.8)	8 (3.9)	78 (37.5)	–	0.008
Fatigue, no. (%)	155 (74.5)	21 (10.1)	140 (67.3)	–	<0.001
Nausea, no. (%)	63 (30.3)	6 (2.9)	41 (19.7)	1 (0.5)	0.063
Vomiting, no. (%)	18 (8.7)	1 (0.5)	7 (3.4)	–	1.000
Mucositis, no. (%)	127 (61.1)	14 (6.7)	81 (38.9)	1 (0.5)	<0.001
Anorexia, no. (%)	54 (30.0)	5 (2.4)	32 (15.4)	–	0.063
Hand and foot syndrome, no. (%)	116 (55.8)	21 (10.1)	86 (41.4)	7 (3.4)	0.003
Dysgeusia, no. (%)	68 (32.7)	1 (0.5)	50 (24.0)	–	1.000
Hypertension, no. (%)	95 (45.7)	19 (9.1)	54 (26.0)	5 (2.4)	0.007
Dyspepsia, no. (%)	42 (20.2)	5 (2.4)	31 (14.9)	–	0.063
Hypothyroidism, no. (%)	77 (37.0)	3 (1.4)	54 (26.0)	–	0.250
Heart failure, no. (%)	4 (1.9)	1 (0.5)	4 (1.9)	–	1.000
Thrombocytopenia, no. (%)	69 (33.2)	16 (7.7)	39 (18.8)	1 (0.5)	<0.001
All events	206 (99.0)	95 (45.7)	196 (94.2)	17 (8.2)	<0.001
Adverse event	Any grade	Grade 3–4			
B)					
Diarrhoea, no. (%)	21 (51.2)	5 (12.2)			
Fatigue, no. (%)	26 (63.4)	2 (4.9)			
Nausea, no. (%)	8 (19.5)	1 (2.4)			
Vomiting, no. (%)	1 (2.4)	–			
Mucositis, no. (%)	14 (34.2)	1 (2.4)			
Anorexia, no. (%)	6 (14.6)	2 (4.9)			
Hand and foot syndrome, no. (%)	15 (36.6)	2 (4.9)			
Dysgeusia, no. (%)	7 (17.1)	–			
Hypertension, no. (%)	8 (19.5)	1 (2.4)			
Dyspepsia, no. (%)	5 (12.2)	–			
Hypothyroidism, no. (%)	11 (26.8)	1 (2.4)			
Heart failure, no. (%)	1 (2.4)	1 (2.4)			
Thrombocytopenia, no. (%)	10 (24.4)	–			
All events	33 (80.5)	11 (26.8)			
C)					
Diarrhoea, no. (%)	24 (11.4)	11 (5.2)			
Fatigue, no. (%)	14 (6.6)	6 (2.8)			
Nausea, no. (%)	4 (1.9)	3 (1.4)			
Vomiting, no. (%)	1 (0.5)	–			
Mucositis, no. (%)	14 (6.6)	3 (1.4)			
Anorexia, no. (%)	1 (0.5)	–			
Hand and foot syndrome, no. (%)	24 (11.4)	15 (7.1)			
Dysgeusia, no. (%)	2 (1.0)	2 (1.0)			
Hypertension, no. (%)	86 (40.8)	1 (0.5)			
Dyspepsia, no. (%)	20 (9.5)	–			
Hypothyroidism, no. (%)	16 (7.6)	15 (7.1)			
Heart failure, no. (%)	3 (1.4)	2 (1.0)			
Thrombocytopenia, no. (%)	8 (3.8)	8 (3.8)			
All events	125 (59.2)	62 (29.4)			

*Comparison between the two phases in terms of grade 3–4 toxicity incidence, by means of McNemar's exact test.
NCI, National Cancer Institute; CTC, Common Toxicity Criteria; TRAEs, treatment-related adverse events.

discussion

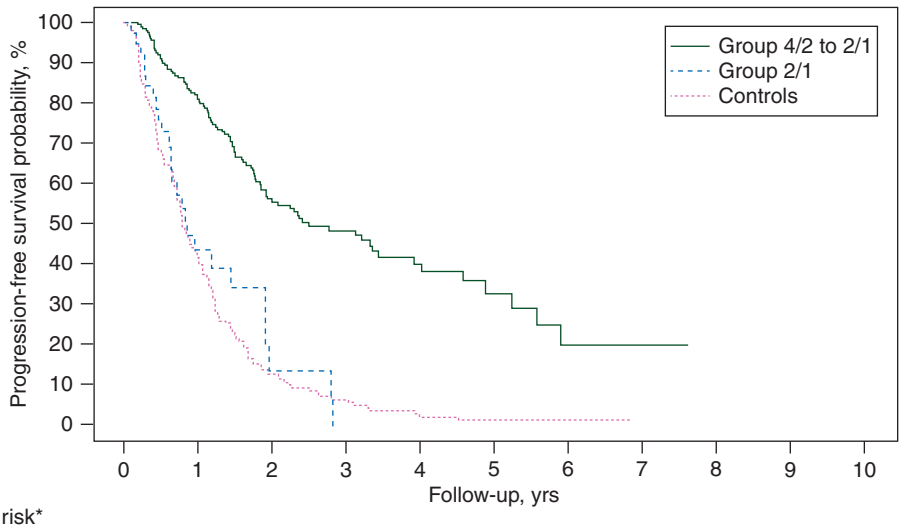
Our analysis suggests that mRCC patients who switched to the 2/1 schedule of sunitinib because of TRAEs during an initial therapy with the standard schedule 4/2 do experience an improved safety profile compared with that observed during the initial period on 4/2 schedule, this allowing to avoid a potentially negative dose reduction in a large proportion of treated cases. A



No. at risk*

Group 4/2 to 2/1	207	172	110	57	32	14	5	1	0	0	0
Group 2/1	39	16	5	4	1	0	0	0	0	0	0
Controls	211	141	82	50	29	20	10	5	2	1	0

Figure 1. Progression-free survival. Asterisk denotes three patients in the 4/2→2/1 group and two patients in the 2/1 group were not evaluable for PFS.



No. at risk*

Group 4/2 to 2/1	205	148	76	41	23	8	3	1	0	0	0
Group 2/1	39	12	2	0	0	0	0	0	0	0	0
Controls	211	81	20	9	3	2	1	0	0	0	0

Figure 2. Overall survival. Asterisk denotes one patient in the 4/2→2/1 group and two patients in the 2/1 group were not evaluable for OS.

significant reduction of overall grade 3–4 toxicities was reported, as well as a reduced incidence of drug-specific toxicities such as fatigue, hypertension, hand–foot syndrome and thrombocytopenia. These adverse events have been reported both in phase III trials and in clinical practice, and can potentially impair the optimal use of sunitinib [18, 19]. Of note, an improved safety profile was also observed in the large subgroup of patients who did not reduce the dose of sunitinib (188/208), clarifying the role of the modified schedule in respect to eventual concomitant dose modification.

Although a direct comparison between different studies can only raise hypotheses for further investigation, our analysis confirms the results of other monocentric experiences [12–16], which showed a better safety profile of sunitinib on a 2/1 schedule, in a larger population of patients representative of daily clinical practice.

Moreover, the switch of sunitinib from a 4/2 to a 2/1 schedule after the onset of clinically relevant toxicities did not appear associated with decreased efficacy. In this study, patients who switched to a 2/1 schedule experienced a longer TD, which can be explained, at least in part, with the reduced incidence of unmanageable toxicities. Obviously, the prolonged PFS observed in this group is affected by several potential biases. First of all, it has been speculated that adverse events observed in the 4/2 phase could be the expression of an increased drug exposure that is directly associated with increased efficacy [20]. In addition, the overall favorable

clinical conditions which characterized the patients who received the 4/2→2/1 schedule—compared with patients who did not change treatment schedule—may have contributed to the increased PFS and OS observed in this subpopulation.

Nevertheless, the PFS observed in this group justifies prospective evaluation of this schedule [20]. The few data deriving from the small group of negatively selected patients starting sunitinib with the 2/1 schedule seem to show an acceptable safety profile, comparable with what observed in the external control group deriving from an international referral center for mRCC.

Despite these encouraging results, our findings should only be considered as preliminary and will require further confirmation in large, prospective, controlled studies. On the other hand, we believe that the safety results are grounded, since our study is, to the best of our knowledge, one of the few studies which also analyzed data from patients who maintained the same dose of sunitinib when they switched to a 2/1 schedule.

It must be acknowledged that our analysis, even if the largest conducted to date on the 2/1 schedule, presents a number of limitations such as its retrospective design—which can affect, for instance, the recording of toxicities, the use of a monocentric external control group, even if deriving from an international referral Center for mRCC, and the observational nature of the analysis. However, it has been suggested that well-conducted observational studies may expand upon the results of clinical trials and shed new lights on the safety and effectiveness of a given intervention in 'real-life' conditions [21, 22]. Data deriving from the small group of patients which started sunitinib on a 2/1 schedule should be regarded with caution, given the small simple size and the negative selection bias of this group, characterized by worse prognostic factors than the other two groups analyzed, although the survival analysis adjusted for the IMDC criteria showed similar results. At least, it should draw caution about starting sunitinib at 2/1 schedule from the initiation of therapy and it should be used only after the development of TRAEs with the standard 4/2 schedule.

Taken these limitations into account, our findings may have relevance for an improvement of clinical practice, in particular with respect to a more personalized treatment of each mRCC patient. In fact, they suggest—using 'real-life' data—the possibility of modifying the standard 4/2 schedule of sunitinib to a better tolerated 2/1 schedule, instead of dose reduction, in patients who experience unmanageable toxicities with the standard regimen. Moreover, this strategy could be also associated with an eventual dose reduction. This possibility widens the options for an individualization of sunitinib treatment, possibly delaying the initiation of a second-line therapy in nonprogressing patients with a poor tolerability. It may be also speculated that an improved safety profile of sunitinib might translate into a PFS benefit, as it allows to maintain increased dosage of sunitinib. On this basis, prospective studies are ongoing (e.g. study NCT02060370) to further investigate the safety and efficacy of switching from a 4/2 to a 2/1 schedule on the basis of occurring toxicity.

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disclosure

SB, Advisory Board member for Novartis, GSK, Pfizer, Exelixis, Janssen, Bayer Schering-Pharma, Astellas, Genentech and BMS; honoraria from Novartis, Pfizer, Bayer Schering-Pharma, Janssen. GP, Advisor Board member for Bayer, Bristol, GSK, Janssen, Novartis; honoraria from Astellas and Pfizer. FM, Advisory Board member for Sanofi, Janseen, Pfizer; honoraria from Novartis, GSK. GDL, Advisory Board member for Novartis, GSK, Janssen, Sanofi, Amgen; honoraria from Novartis, Pfizer, Janssen. CP, consultancy agreement with Pfizer, Novartis, GSK, Bayer Schering and Astellas; research grants from Pfizer. AC, Honoraria from Pfizer, Novartis, GSK. BE, consultancy agreement with Pfizer, Novartis, GSK, Bayer. AM, honoraria from GSK, Pfizer, Novartis, Sanofi, Bayer. RS, Advisory Board member for GSK, Novartis, Bayer, Astellas, Janssen; honoraria from Novartis, Pfizer, Bayer, GSK, Janssen, Sanofi. GLC, honoraria from Novartis and Pfizer. DS, Advisory Board member for Novartis, GSK, Janssen, Sanofi, Amgen, Roche. CB, research grants from Sanofi, Roche, Merck Serono, Glaxo and Celgene. EV, honoraria Pfizer, Novartis, Janssen. All remaining authors have declared no conflicts of interest.

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appendix

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Prospective study evaluating the relative sensitivity of ^{18}F-NaF PET/CT for detecting skeletal metastases from renal cell carcinoma in comparison to multidetector CT and ^{99m}Tc-MDP bone scintigraphy, using an adaptive trial design

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Background: The detection of occult bone metastases is a key factor in determining the management of patients with renal cell carcinoma (RCC), especially when curative surgery is considered. This prospective study assessed the

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