REVIEW

How clinical practice is changing the rules: the sunitinib 2/1 schedule in metastatic renal cell carcinoma

ABSTRACT

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Introduction: Currently, sunitinib is a standard of care in first-line treatment for metastatic renal cell carcinoma (mRCC). However, with the standard 4/2 schedule (sunitinib 50 mg/day; 4 consecutive weeks on treatment; 2 weeks' rest), 50% of patients require dose reductions to mitigate toxicity, highlighting the need to investigate alternative dosing schedules that improve tolerability without compromising efficacy.

Areas covered: We present a concise critical review of published studies comparing the efficacy and safety of the 4/2 and 2/1 schedule (2 weeks on treatment; 1 week rest) for sunitinib. While all studies evaluating the 2/1 schedule have a low level of evidence, the results indicate that the 2/1 schedule improves tolerability compared with the 4/2 schedule, including significant reductions in the incidence of specific adverse events. It was not possible to make any definitive conclusions regarding efficacy due to methodologic limitations of these studies.

Expert commentary: In the absence of strong evidence supporting the safety and efficacy of the 2/1 schedule, we recommend that patients should be initiated on sunitinib therapy with the standard 4/2 schedule and only be switched to the 2/1 schedule after the development of dose-limiting toxicities from weeks 3–4 (cycle 1) of the 4/2 schedule cycle.

KEYWORDS

Angiogenesis inhibitors; renal cell carcinoma; standard of care; sunitinib; dose schedule

1. Introduction

Sunitinib is an oral, multitargeted tyrosine kinase inhibitor with anti-angiogenic and antitumor activity[1, 2, 3, 4].In a landmark Phase III study of treatment-naïve patients with metastatic renal cell carcinoma (mRCC), sunitinib resulted in a median progression-free survival (PFS) of 11 months compared with only 5 months for interferon-α, and a median overall survival (OS) extending beyond 2 years for the first time [5, 6].On the basis of these results, sunitinib became one of the standards of care for first-line therapy of mRCC and the most commonly prescribed agent in this setting [7, 8]; however, the optimal dose and schedule of sunitinib is still not well defined.

The current label for sunitinib recommends the 4/2 dosing schedule (sunitinib 50 mg/day; 4 consecutive weeks on treatment, followed by 2 weeks' rest), with dose adjustments and interruptions being based on individual safety and tolerability [9, 10]. Phase I data recommended this schedule, based on dose-limiting toxicities that included fatigue, hypertension and skin toxicity [11, 12]. Toxicity data from subsequent Phase III trials showed that grade 3–4 treatment-related adverse events were common, including fatigue (11–17%), diarrhea (8–9%), hand–foot syndrome (9–11%) and neutropenia (16–19%); approximately 20% of patients discontinued sunitinib due to adverse events [5, 6, 13].

In a pharmacokinetic/pharmacodynamic meta-analysis in patients receiving sunitinib for different cancer types, including mRCC, increased systemic exposure to sunitinib was associated with improved patient outcomes, including longer time to progression (TTP), longer OS, and greater tumor response rates, but also an increased risk of adverse events [14].

These results highlight the conundrum facing clinicians: what is the sunitinib dosing schedule that delivers the optimal benefit–risk balance for patients with mRCC? Although the standard 4/2 schedule has been shown to be efficacious in this setting, approximately 50% of patients require dose reductions [6, 13], which will lower both dose intensity and drug exposure. Given the relationship between exposure and efficacy [14], dose reductions could have an overall negative impact on patient outcomes [15, 16].

These considerations inspired efforts to identify alternative sunitinib dosing schedules with improved tolerability without compromising drug exposure and consequent clinical outcome [17, 18, 19]. A Phase II trial of a continuous 37.5 mg daily dosing schedule showed an acceptable safety profile [20], but a randomized Phase II trial failed to demonstrate an advantage in efficacy or safety over the 4/2 schedule [21]. Another schedule that has been the subject of much attention is the sunitinib 50 mg 2/1 schedule (2 weeks treatment followed by 1 week rest). The first phase I trial of a 2/1 schedule was published by Britten et al. [22], who reported a safety profile comparable to the 4/2 schedule. Several recent studies of the 2/1 schedule consistently demonstrated lower toxicity and a lower incidence of dose interruption or dose reduction compared with the 4/2 schedule [23, 24, 25, 26, 27, 28, 29, 30]. However, it must be noted that most of these studies are retrospective, single-center database analyses of patient-level data, and, as such, are susceptible to considerable bias in data selection and analysis [31].

The lower toxicity and comparable dose intensity of the 2/1 schedule compared with the standard 4/2 schedule is supported by the results of pharmacokinetic studies. A key finding was that the overall average plasma exposure to sunitinib and its active metabolite is similar with the 2/1 and 4/2 schedules [32]. Sunitinib plasma concentrations reach a steady state within 14 days of treatment initiation [11, 12, 22], at which point maximum anti-angiogenic activity is achieved [24]. The time point at which steady-state plasma concentrations of

sunitinib are achieved coincides with the first appearance of treatment-related adverse events, which steadily worsen thereafter [30]. Studies to investigate the safety and efficacy of pharmacokinetic-guided dosing of the 2/1 and 4/2 schedules are required [33].

In the absence of consensus guidelines on optimizing sunitinib dosing for patients with mRCC, we set out to provide a concise overview of the available evidence of the impact of sunitinib dosing schedules on clinical outcomes. We present here a critical review of four recent studies that compared the efficacy and safety of the sunitinib 2/1 and 4/2 schedules [23, 25, 27, 28].

2. Review of studies

The majority of published studies on the 4/2 sunitinib dosing schedule were excluded from this analysis due to suboptimal or unclear methodology (Table 1). Four studies were selected for critical review; the design characteristics and key results for each of these studies are summarized in Table 2.It should be noted that all four studies have a low level of evidence.

2.1. Atkinson et al. (2014) [23]

2.1.1. Study design

This study was a retrospective, single-center database study of patients with mRCC who received first-line sunitinib therapy. Patients who experienced an intolerable adverse event on the traditional 4/2 schedule were switched to an alternative schedule, including the 2/1 schedule (82%), 1 week on/3 days off alternating with 1 week on/4 days off (8%), and another, unspecified schedule (10%).Patients were assigned to the 4/2 or alternative group according to the schedule at the time of sunitinib discontinuation. No primary endpoints were specified.

2.1.2. Patients and treatment

Data from 185 patients were analyzed. At baseline, 161 (87%) were assigned to the 4/2 group and 24 (13%) were assigned to the alternative group. Across the duration of the study, 98 patients (53%) were maintained on the 4/2 schedule and 87 (47%) were initiated on or switched to an alternative schedule due to adverse events. Sunitinib dose intensity after transition to an alternative schedule was maintained at 50 mg/day in 79% of patients; 21% received less than 50 mg/day.

2.1.3. Efficacy

Median treatment duration (TD) was 4.1 months in patients maintained on 4/2compared with 13.6 months in patients initiated on or switched to an alternative schedule (p<0.0001).Median OS was 17.7 months on 4/2 compared with 33.0 months on an alternative schedule (p<0.0001). Median PFS in patients on 4/2 was 4.3 months compared with 14.5 months on an alternative schedule (p <0.0001).

2.1.4. Adverse events

Common adverse events (frequency>20%)resulting in a switch from 4/2 to an alternative schedule included fatigue (n = 40, 64%), hand–foot syndrome (n = 24, 38%), diarrhea (n = 20,32%) and mucositis (n = 14,22%). The frequency of these adverse events was markedly reduced after switching to an alternative schedule: fatigue (n = 18, 29%), hand–foot syndrome (n = 6, 10%), diarrhea (n = 4, 6%) and mucositis (n = 3, 5%). An analysis of the incidence of grade 3–4 toxicities between the two groups was not performed.

2.1.5. Critical assessment

A weakness of the study is the alternative schedule group including patients on three different dosage schedules. Although the 2/1 schedule was the predominant alternative schedule (82%), the existence of this heterogeneity makes data interpretation difficult. Although large differences in OS and PFS were observed between the 4/2 and 2/1 schedule groups, these results must be interpreted with caution because of the inherent limitations of the retrospective database design. These include bias in data selection and analysis, missing data and the lack of quality control of the data [31]. In addition, the survival figures for the standard sunitinib dose and schedule were particularly low. A subgroup analysis of patients initiated on an alternative schedule at baseline was conducted to investigate the possibility of survival bias caused by switching from the traditional 4/2 schedule to an alternative schedule. This analysis found that OS and PFS were comparable to that achieved with the full dataset, arguing against major survival bias. Despite these limitations, the results from this study indicate that the 2/1 schedule mitigates the toxicity associated with sunitinib therapy.

2.2. Bracarda et al. (2015) [25]

2.2.1. Study design

This was a retrospective, multicenter database analysis of patients with mRCC who were treated with first-line sunitinib. There were three treatment groups: (i) the 4/2 to 2/1 group comprised patients who started on the 4/2 schedule and switched to the 2/1 schedule due to intolerable adverse events; (ii) the 2/1 group comprised patients who started with the 2/1 schedule mainly because of suboptimal clinical conditions; and (iii) the4/2 control group comprised patients treated with the standard 4/2 schedule in another institution. Safety was the primary endpoint.

2.2.2. Patients and treatment

Data from a total of 460 patients were analyzed: 208 patients in the 4/2 to 2/1 group, 41 patients in the 2/1 group and 211 patients in the external 4/2 control group. In the 4/2 to 2/1 group, 188 patients (90.4%) started on the standard sunitinib 50 mg/day dosage, whereas 106 of these 188 (56.4%) patients were maintained at 50 mg/day after switching. In the 2/1 group, 30 of 41 cases (73.2%) started sunitinib at the 50 mg/day dosage.

2.2.3. Efficacy

In the 4/2 to 2/1 group, the median overall TD was 28.2 months. Within this group, median TD was 4.3 months on the initial 4/2 schedule and 19.7 months on the subsequent 2/1 schedule. In the 2/1 and 4/2 control groups, median TD was 7.8 months and 9.7 months, respectively.

Median OS was not reached in the 4/2 to 2/1 group, but was 23.2 months in the 2/1 group and 27.8 months in the 4/2 control group. Overall 36-month survival rates were 72.7%, 32.0% and 42.3%, respectively. Median PFS was 30.2 months, 10.4 months and 9.7 months, respectively.

2.2.4. Adverse events

The overall incidence of grade 3–4 adverse events was significantly reduced after switching to the 2/1 schedule: from 45.7% in the 4/2 phase versus 8.2% in the 2/1 phase ($p<0.001$).

2.2.5. Critical assessment

The results suggest that switching from the 4/2 to the 2/1 schedule may be associated with increased efficacy. However, it is difficult to rule out the possibility that clinical characteristics of the 4/2 to 2/1 group may have contributed to the increased efficacy compared with the 4/2

control group. Furthermore, data from the 2/1 group should also be regarded with caution, given the small sample size and the negative selection bias of this group, which was characterized by ‘suboptimal clinical conditions’. With respect to tolerability, patients who switched to the 2/1 schedule after initial therapy with the 4/2 schedule experienced a significant reduction in the overall incidence of grade 3–4 toxicities. In summary, despite its limitations, the results from this study suggest that the 2/1 schedule may mitigate the toxicity associated with sunitinib therapy.

2.3. Najjar et al. (2014) [27]

2.3.1. Study design

This was a retrospective, single-center database study of patients with mRCC who switched from sunitinib schedule 4/2 to 2/1.

2.3.2. Patients and treatment

Of 170 patients with mRCC treated during an 8-year period (2004–2012), a total of 30 patients were identified who initially received the 4/2schedule but were subsequently switched to the 2/1 schedule. Patients remained on the 4/2 schedule for a median of 12.6 months (range 1.2–61.2) prior to being switched. Of note, more than half (53%) of patients who started on schedule 4/2 had their dose reduced due to toxicity prior to switching to the 2/1 schedule.

2.3.3. Efficacy

Median PFS overall was estimated to be 43.9 months, measured from the start of sunitinib therapy on schedule 4/2. No comparative PFS data were presented for schedule 4/2 versus 2/1.

2.3.4. Adverse events

In general, the incidence of all grade and grade 3–4 toxicity was lower on schedule 2/1 than on 4/2.Two of the most common adverse events, fatigue and hand–foot syndrome, were significantly less frequent on schedule 2/1 (53% and 17%) than on schedule 4/2 (70% and 50%,*p* =0.0003 and *p* =0.0004, respectively), as were mucositis and thrombocytopenia (*p* = 0.03, both).

2.3.5. Critical assessment

The limitations of this study are those inherent in its retrospective design, small sample size and single-center nature. A key point is that more than half (16 of 30, 53%) of the patients on the initial 4/2 schedule required dose reduction prior to switching to the 2/1 schedule: 15patients to 37.5 mg/day and one to 25 mg/day. The inclusion of dose-reduced patients in the analysis prevented a meaningful comparison of the toxicity of the two schedules, as the dose intensity before and after switching schedules was not comparable. No efficacy data were presented; however, the results of this study appear to be consistent with previous studies in showing reduced toxicity on schedule 2/1 compared with schedule 4/2.

2.4. Lee et al. (2015) [28]

2.4.1. Study design

This was a multicenter, randomized, open-label, Phase II trial of sunitinib therapy in treatment-naïve patients with mRCC. Patients were randomly assigned to sunitinib 4/2 or 2/1 schedules after stratification by Memorial Sloan Kettering Cancer Center risk grouping (favorable, intermediate, poor) [34] and the presence or absence of measurable lesions. The primary endpoint was the 6-month failure-free survival (FFS) rate, determined by intention-to-treat analysis. Failure was defined as discontinuation of sunitinib therapy for any reason, including disease progression, treatment toxicity, patient refusal or death.

2.4.2. Patients and treatment

A total of 74 eligible patients were randomly assigned to the two treatment groups: 36 to the 4/2 group and 38 to the 2/1 group. The proportion of patients who underwent dose reduction within 6 months after initiation of treatment was 21% in the 2/1 group compared with 50% in the 4/2 group ($p = 0.01$).

2.4.3. Efficacy

The primary endpoint, FFS at 6 months, was higher in the 2/1 group (63%, 24/38) than in the 4/2 group (44%, 16/36). Median time to treatment failure was 7.6 months and 6.0 months, respectively ($p = 0.029$). Median OS was 30.5 months and 28.4 months and median TTP was 12.1 months and 10.1 months. The objective response rate (ORR) was 47% in the 2/1 group and 33% in the 4/2 group.

2.4.4. Adverse events

Neutropenia and fatigue were less frequently reported in the 2/1 group than in the 4/2 group (61% and 83%, and 31% and 58%, respectively; $p = 0.037$ and $p = 0.017$). Other common adverse events that were reported less frequently in the 2/1 group than in the 4/2 group included stomatitis, skin rash and hand–foot syndrome.

2.4.5. Critical assessment

This is the only prospective trial published to date that has evaluated the efficacy and safety of the sunitinib 2/1 versus4/2 schedules. The main findings were a higher FFS and a lower incidence of adverse events in patients treated with the sunitinib 2/1 schedule in respect to cases treated with the 4/2 schedule. The authors correctly noted the major study limitations.

The small sample size, despite the greater than 6 years of patient accrual, meant that it was not adequately powered to detect clinically significant differences in OS, ORR and TTP. The open-label design was susceptible to bias as patients may have switched over to the 2/1 schedule due to an awareness that it could provide better tolerability than the 4/2 schedule. The primary endpoint in the study, FFS, was defined as discontinuation of sunitinib therapy for any reason. However, as no data were presented on the proportion of failures due to disease progression, toxicity, patient refusal or death, it is difficult to interpret the FFS results. Furthermore, it is not clear why data for a more established clinical endpoint, such as PFS, were not reported. In summary, putting the caveats associated with the FFS efficacy data aside, this study shows that the sunitinib 2/1 schedule is associated with lower toxicity than the 4/2 schedule without compromising efficacy.

3. CONCLUSIONS

Although the sunitinib 4/2 schedule is the reference schedule for first-line treatment of mRCC [35, 36], half of patients receiving this approved schedule require dose reductions due to relevant toxicities [5, 6, 13] that could compromise patient outcomes [15, 16]. The alternative 2/1 dosing schedule was instigated to reduce toxicity whilst maintaining dose intensity and therefore efficacy. Indeed, a dose intensity below 0.7 and dose discontinuations during all landmark periods were associated with significantly shorter survival time in a retrospective chart review conducted at ten tertiary oncology centers in Europe [37]. The results from all studies reported to date, including the four studies reviewed in detail here, suggest that the 2/1 schedule improves sunitinib tolerability compared with the 4/2 schedule. In patients who switched to the 2/1 schedule, a significant reduction was observed in the incidence of specific adverse events, including fatigue, hand–foot syndrome and neutropenia. Switching from the 4/2 to the 2/1 schedule does not appear to compromise efficacy, as measured by PFS; however, it is not possible to make any definitive conclusions regarding efficacy because of the limitations of the studies that all have a low evidence level.

The increasing use of the sunitinib 2/1 schedule is a good example of how oncologists modify the indicated dosing of oral anticancer drugs according to real-world clinical practice [15]. Indeed, the 2/1 schedule might be considered to be an evolution of therapy management, given that the sunitinib summary of product characteristics allows for dose reductions or interruptions [30], which are themselves forms of schedule modification. Although the sunitinib 2/1 treatment schedule is widely used in clinical practice [17, 18], Lee et al. [28], one of the four studies reviewed here, is the only randomized prospective study comparing the 2/1 and 4/2 schedules that has been published to date. A prospective, open-label, multicenter, Phase II study (NCT02060370) is in progress to assess the incidence of grade 3 toxicities on the 2/1 schedule compared with published data on the 4/2 schedule. The SURF study is another ongoing randomized Phase II study evaluating the safety and efficacy of changing dose schedule versus decreasing the dose of sunitinib in patients with mRCC experiencing toxicity on the 4/2 schedule. The primary endpoint of the study, which will enroll 248 patients, is to determine the duration of treatment in both arms (NCT02689167).

Although these studies will provide much-needed prospective data, it is clear that a well-designed, head-to-head trial of the safety and efficacy of the 4/2 and 2/1 schedules is urgently needed.

In the absence of strong evidence supporting the safety and efficacy of the 2/1schedule, we recommend that patients should be initiated on sunitinib therapy with the standard 4/2 schedule and only be switched to the 2/1 schedule, as an alternative or in addition to dose reductions, after the development of dose-limiting toxicities. As AEs increase during each

cycle and are worse in the third and fourth weeks [38], we recommend that patients are assessed with a view to starting the 2/1 schedule from cycle 1, weeks 3–4**.**

EXPERT COMMENTARY

Currently, sunitinib is a standard of care in first-line treatment for mRCC. Given that treatment efficacy with sunitinib therapy is closely linked to dose intensity and drug exposure, a key challenge faced by clinicians is finding the right dosing schedule to deliver the optimal benefit–risk balance for patients. Minimizing treatment-related toxicities, such as fatigue, hand–foot syndrome and diarrhea is critical to allow maximum exposure. In this regard, the 2/1 dosing schedule for sunitinib has shown promise as a strategy to improve the tolerability of sunitinib therapy, although the available data are currently insufficient to determine whether equivalent efficacy is maintained with this approach. In order to achieve more clarity on this issue, the results of prospective, randomized studies evaluating alternative sunitinib dosing regimens are needed.

While these alternative dosing regimens could provide significant benefit to patients who are unable to tolerate the standard 4/2 schedule, this also does not mean that all patients should be started on an alternative dosing regimen. However, this alternative schedule is currently extensively used as a way to handle the toxicities occurring with the 4/2 schedule, or even as initial dosing. Indeed, the variation in tolerability seen with sunitinib is thought to be linked to each individual patient’s ability to metabolize sunitinib and, as such, there has been recent interest in pharmacokinetic-guided dosing of sunitinib, which is another area where further clinical research could be warranted. Being able to more accurately predict which patients are most likely to benefit from a specific dosing regimen could help ensure that more patients are started on the optimal dose of sunitinib, and are achieving maximal clinical benefit from therapy. Our analysis and conclusions are limited to patients with mRCC.

FIVE-YEAR VIEW

Treatment of mRCC has been evolving rapidly in the past 10 years, especially with the development of vascular endothelial growth factor- (VEGF) and mechanistic target of rapamycin- (mTOR) inhibitors. These improvements have been particularly rapid in the last year, with the approval of three new treatments in the second-line setting (nivolumab, cabozantinib, and lenvatinib + everolimus). Although the first-line setting has not changed recently, sunitinib is currently being challenged in numerous ongoing Phase III studies, either by combination of check-point inhibitors and VEGF inhibitors (tyrosine kinase inhibitors or bevacizumab), or by a combination of two check-point inhibitors (nivolumab and ipilimumab). In this regard, in 5 years' time, if these new combinations are demonstrated to be superior to sunitinib 4/2 as used in the ongoing Phase III studies, and if in the same period the sunitinib 2/1 schedule is shown to be superior to the 4/2 classical schedule, there will be many discussions about what will be the best first-line treatment option.

KEY ISSUES

- The incidence of treatment-related toxicities with the standard 4/2 schedule of sunitinib remains a challenge for patients to maintain the level of drug exposure required for optimal treatment efficacy
- Alternative dosing strategies, such as the 2/1 dosing schedule of sunitinib, are currently used to improve treatment tolerability without compromising efficacy
- Although the clinical studies evaluating the 2/1 sunitinib schedule to date have generally a low level of evidence, there is a large consensus that this new schedule reduces toxicity
- While efficacy does not appear to be compromised with the 2/1 dosing schedule, the results of prospective, randomized studies of this treatment regimen are needed to fully evaluate this treatment approach

- Until the results of such studies are available, it is recommended that patients should start on the 4/2 schedule and can be switched to 2/1 if dose-limiting toxicities occur

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43. Miyake H, Harada K, Miyazaki A, Fujisawa M. Improved health-related quality of life of patients with metastatic renal cell carcinoma treated with a 2 weeks on and 1 week off schedule of sunitinib. Med Oncol 2015;32:78.

44. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–394.

Table 1. Published reports on the alternative sunitinib dosing schedule excluded from this analysis.

Study	Reasons for not including in analysis
Published studies	
Gyergyay et al. [39]	Congress report only, single center with small number of patients
Neri et al. [29]	False prospective design, unclear methodology, single center with a small heterogeneous patient population
Bjarnasonet al. [24]	Method enables identification of patient selection bias, retrospective design, small heterogeneous patient population
Cheng et al. [40]	Congress report only, retrospective design
Kondo et al. [26]	Arbitrary switching of schedules by investigators, small number of patients, retrospective design
Ohzeki et al. [41]	Considerable patient selection bias, small number of patients, retrospective design

Togo et al. [42]	Prospective study but has low PFS/OS and high thrombocytopenia, small number of patients
Miyake et al. [43]	Retrospective design, small number of patients

OS: overall survival; PFS: progression-free survival.

Table 2. Study characteristics and key findings

Study	Design	Primary endpoint	Patients, n	Evidence level [44]	Efficacy (4/2 vs 2/1)	Toxicity (4/2 vs 2/1)
Atkinson et al. [23]	Retrospective, single-center database study	N/R	185	Low	• Median TD: 4.1 (95% CI: 2.9–4.7) vs 13.6 (95% CI: 9.4–16.1) months* • Median OS: 17.7 (95% CI 10.8–22.2) vs 33.0 (95% CI 29.3–N/E) months* • Median PFS: 4.3 (95% CI: 3.4–6.4) vs 14.5 (95% CI: 11.3–19.4) months*	AE frequency: • Fatigue: 64% vs 29% • Hand–foot syndrome: 38% vs 10% • Diarrhea: 32% vs 6% • Mucositis: 22% vs 5% • Nausea: 14% vs 11%
Bracarda et al. [25]	Retrospective, controlled, multicenter database study	Safety	460	Low	• Median TD: 4.3 (IQR 2.0–12.0) vs 19.7 (IQR 7.3–N/E) months • Median PFS: 9.7 (95% CI: 8.9–11.7) vs 30.2 (95% CI: 23.2–	• Incidence of grade ≥3 toxicities: 45.7% vs 8.2%*

					47.1) months	
Najjar et al. [27]	Retrospective, single-center database study	N/R	30	Very low	• N/R	• Grade 3–4 toxicities: 97% vs 27%*
Lee et al. [28]	Multicenter, randomized, open-label, Phase II trial	FFS[†]	74	Low	• 6-month FFS: 44% vs 63% • Median TTF: 6.0 vs 7.6 months[‡] • Median OS: 28.4 vs 30.5 months • Median TTP: 10.1 vs 12.1 months • ORR: 33% (95% CI: 18–49) vs 47% (95% CI: 32–63)	• Neutropenia: 61% vs 37% • Fatigue: 83% vs 58%

AE, adverse event; CI, confidence interval; FFS, failure-free survival; IQR, interquartile range; N/E, not estimable; N/R, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TD, treatment duration; TTF, time to treatment failure; TTP, time to progression.

*p <0.0001.

[†]Failure was defined as discontinuation of sunitinib therapy for any reason, including disease progression, treatment toxicity, patient refusal or death [28].

[‡]p <0.05.