Safety and effectiveness of classical and alternative sunitinib dosing schedules for metastatic renal cell carcinoma: a meta-analysis

Seye Abogunrin^{*1}, Ajibade O Ashaye², Joseph C Cappelleri³, Andrew G Clair⁴, Kyle Fahrbach⁵, Krishnan Ramaswamy⁴, Lucile Serfass⁶, Sandy Srinivas⁷, Despina Thomaidou⁸ & Giovanni Zanotti⁴

¹Meta Research, Evidera, London, W6 8BJ, UK

²Formerly Meta Research, Evidera, Waltham, MA 02451, USA

³Pfizer Inc, Groton, CT 06340, USA

⁴Pfizer, Inc., New York, NY 10017, USA

⁵Meta Research, Evidera, Waltham, MA 02451, USA

⁶Pfizer Oncology, 75668 Paris, France

⁷Stanford University Medical Center, Stanford, CA 94304, USA

⁸Pfizer, 15451 Athens, Greece

*Author for correspondence: Tel.: +44 (0)208 576 5049; seye.abogunrin@evidera.com

The optimal dosing schedule to maintain the effectiveness of sunitinib for metastatic renal cell carcinoma – while reducing toxicity – remains an important clinical question. A meta-analysis of randomized trials and observational studies assessed the relative treatment effects of 4/2, 2/1 and transitional-2/1 schedules on outcomes and adverse events using Bayesian network meta-analysis methods. Treatment with 2/1 reduced the risk of disease progression or death by 25% and had lower odds of hand-and-foot syndrome compared with the 4/2. A numerical but not ‘statistical’ benefit in progression-free survival was observed with the transitional-2/1 compared with 4/2. Alternative schedules with the 2/1 and transitional-2/1 may be more clinically beneficial in metastatic renal cell carcinoma than the 4/2 schedule.

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Over 270,000 new cases of renal cell carcinoma (RCC) are diagnosed every year accounting for about 90% of kidney cancers [1,2]. The economic impact of treating metastatic clear cell renal cell carcinoma (mRCC), which constitutes about one in every three RCC cases at diagnosis, is estimated to be approximately US\$1.6 billion in some selected countries [3]. The introduction of target agents, mainly tyrosine kinase inhibitors (TKIs) of VEGF receptors, have improved outcomes for patients with mRCC [4,5] in the last decade. The recent introduction of novel immunotherapeutic agents has provided important additional benefits [6–9]. However, VEGFR TKIs currently remain a mainstay of RCC treatment, and continue to play an important role in the management of treatment-naïve and pretreated patients.

Sunitinib is an oral, multitargeted TKI with antiangiogenic and antitumor activity. A pivotal Phase III study of treatment-naïve patients with mRCC determined sunitinib prolonged median progression-free survival (PFS) and objective response rate (ORR) compared with IFN- α . It also extended median overall survival (OS) beyond 2 years for the first time in the history of mRCC [10,11]. Based on these results, sunitinib has become one of the standards of care for treatment-naïve patients with mRCC, and is currently the most commonly used agent in this setting [12].

Sunitinib is administered to patients with mRCC on a schedule of 4 weeks on with a 2-week break before the next dose (hereafter referred to as ‘classical 4/2 schedule’). This 2-week break is intended for patients’ recovery from known toxicities of the conventional 4-week daily dose. The classical 4/2 schedule has been shown to cause high incidences of adverse events (AEs) in Phase III clinical trials and clinical practice, including fatigue,

diarrhea, stomatitis, hematological toxicity and hand-foot syndrome. Consequently, its use frequently requires dose reductions and/or treatment interruptions or discontinuation [11,13–15].

Unnecessary dose reductions and/or treatment interruptions could result in the lowering of dose intensity and drug exposure, which may compromise efficacy [16]. Considering these risks, alternative treatment schedules have been explored in real-world practice including a 2-week on with a 1-week break (hereafter referred to as ‘alternative 2/1 schedule’) schedule and a transition from the classical schedule to the alternative schedule (hereafter referred to as ‘transitional 2/1 schedule’) in patients experiencing relevant toxicities. It is commonly known that sunitinib is most effective when given to patients with mRCC at the full dosage of 50 mg daily [16], but the optimal schedule to maintain its demonstrated activity, while minimizing toxicity is not yet established, despite several studies evaluating the role of alternative sunitinib schedules [17–20]. Therefore, we conducted a systematic literature review (SLR) and meta-analysis (MA) to assess the safety and effectiveness of the classical 4/2, alternative 2/1 and transitional 2/1 sunitinib dosing schedules, to provide treatment recommendations in patients with mRCC who are or may be unable to tolerate the classical 4/2 schedule.

Methods

Systematic literature review

The SLR was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. A protocol was developed for this SLR; however, it was not preregistered or registered publicly.

Identification & selection of studies

The Cochrane Collaboration Central Register of Controlled Trials, Embase and MEDLINE were searched to identify studies published up to November 2017 using keywords synonymous with ‘renal cell carcinoma’ and ‘sunitinib’. The American Society of Clinical Oncology (ASCO), the ASCO Genitourinary Cancers Symposium (GU) and bibliographies of SLRs were also searched, with, to identify other publications of potential relevance. Studies were eligible if they were Phase II and III randomized controlled trials (RCTs) or longitudinal observational studies with a comparative design. They were also eligible if the studies reported data on safety and effectiveness outcomes in patients with mRCC treated with the classical 4/2 or any alternative 2/1 dosing schedule, and if they were published in English. The search strategies and prespecified study selection criteria can be found in the Supplementary Information (Supplementary Tables 1–5).

The study selection criteria were used by two reviewers to screen the titles, abstracts and full texts for relevance to the SLR. Any discrepancies were resolved by a third reviewer.

Data extraction

For each study included in the review, details of the study design, patient characteristics, interventions and outcomes were extracted by one reviewer and quality checked for accuracy and correctness by another reviewer.

Meta-analyses

Feasibility assessment

A feasibility assessment was conducted, prior to conducting the MA on the included studies, to determine whether there was sufficient, available data amenable for analysis and exploration of potential sources of heterogeneity within the studies. The viability of creating a network of included studies was assessed by determining whether the included studies were comparable with regards to study setting, design, treatment, patient characteristics and outcome definitions. Observational studies considered in the feasibility assessment were also qualitatively assessed for sampling bias by checking for the presence of patient channeling, which we defined as prescribing an intervention to a preferred group of patients that will likely benefit from that treatment [22].

Meta-analytical methods

Mixed treatment comparisons [23,24] of the three dosing schedules, identified as classical 4/2, transitional 2/1 or alternative 2/1, were conducted using Bayesian methods to obtain relative treatment effects. This involved indirect and pairwise MAs as well as network meta-analyses (NMAs) of all outcomes that were deemed analyzable. The results were presented for both sets of analyses. NMAs are typically conducted on randomized data, but an NMA was performed on non-randomized data to compare the classical 4/2 schedule with the transitional 2/1 schedule

because data from RCTs were unavailable. Random- and fixed-effects models were employed when appropriate, and analyses were limited to fixed-effects models in cases where there was limited information to estimate a random-effects variance. Otherwise, results of random-effects models were presented.

Statistical heterogeneity was quantified using the I^2 statistic [25]. Two sensitivity analyses that excluded outlier data were conducted for each of the time-to-event effectiveness outcomes. The first sensitivity analysis excluded data for OS and PFS reported for any dosing schedules from the only RCT identified by the SLR – Lee *et al.* [26]. The second used data, also for OS and PFS, from all patients randomized to the classical 4/2 schedule arm of the RCT.

The relative effects for OS and PFS were estimated with hazard ratios (HRs) and their associated 95% credible intervals (CrIs). Time-to-treatment progression (TTP) data were used as proxy in one instance for PFS due to a lack of data [26]. ORR, partial response (PR), complete response (CR), stable disease (SD), progressive disease (PD) and grade 3–4 AEs were assessed and presented as odds ratios (ORs) and their associated 95% CrIs. A statistical advantage was demonstrated if the CrIs did not cross 1, while trends for the treatment and comparator arms were demonstrated when CrIs crossed 1 but HRs or ORs were <0.80 and >1.25 , respectively.

All analyses were conducted using OpenBugs 3.2.2.

Results

Systematic literature review

Of 692 unique records reviewed, full texts of 11 primary studies (12 publications) met the SLR protocol's prespecified inclusion criteria. No additional publications were identified from the conference or bibliography searches (Supplementary Figure 1 in Supplementary Appendix). Most studies were of retrospective cohort design with data sourced from medical records. Only two clinical trials were identified, one comparative, nonrandomized Phase II trial [27] and one multicenter, Phase II RCT [26]. Study samples ranged from 30 to 460 patients across four continents. Four studies each were identified for Asia and North America, while one study each reported data on populations from Africa and Europe. The last study did not provide details of the geographic location.

Meta-analysis

Feasibility assessment

Nine [26–35] of the 11 studies provided evidence on safety and effectiveness outcomes that was deemed eligible for comparison via NMA (Table 1; Figure 1). Meta-analyzable effectiveness outcomes were OS, PFS, ORR, CR, PR, SD and PD. Safety outcomes contributing to the NMA were grade 3–4 AEs inclusive of fatigue, nausea, diarrhea, thrombocytopenia, leukopenia, anemia, neutropenia and hand-foot syndrome. The populations were broadly similar across the nine studies in terms of age, gender, Eastern Cooperative Oncology Group (ECOG) status and Memorial Sloan Kettering Cancer Center (MSKCC) risk group. Patient recruitment periods spanned a decade from October 2004 to September 2014.

Two observational studies were considered ineligible for the MA as they did not compare at least two of the dosing schedules of interest. While both studies included patients who had received the classical 4/2 schedule, one included patients who received a variety of alternative schedules – namely 2/1 (82%), 7 days on and 3 days off alternating with 7 days on and 4 days off (8%) and another alternative schedule (details not reported; 9%) [17] – and the other included patients who received continuous daily dosing as well as other alternative schedules, specific details of which were not reported [33]. Table 1 provides an overview of the dosing schedules evaluated in the included studies.

Definitions of OS were similar across four studies (i.e., the time between enrollment and death from any cause). PFS was defined as time from enrollment to the occurrence of disease progression or death from any cause in the six studies when this outcome was assessed. Lee *et al.* [26] did not report data on PFS. TTP was considered the most similar outcome and was therefore used as a proxy for PFS.

MA results: alternative 2/1 versus classical 4/2 schedule

Effectiveness

Treatment with the alternative 2/1 schedule prolonged PFS in the base-case analysis compared with treatment with the classical 4/2 schedule (HR: 0.75 [95% CrI: 0.60–0.94]). Additional sensitivity analyses did not find any statistical advantages for either schedule. No 'statistical differences' were found in OS between the dosing schedules observed in base-case or sensitivity analyses. There were also no statistical differences observed between dosing

Table 1. Overview of trials included in the network meta-analysis.

Data source Registry Trial name	Country	Study design	Dosing schedule	Initial (maint.) dose	Treatment duration	Follow-up time (months)	Age (range)	Male (%)	ECOG status (0/1/2/≥2; %)	MSKCC status: Fav. Intermed. Unfav. (%)	HRG: Fav. Intermed. Unfav. (%)	Histology clear cell/ Papillary Other (%)	Metastatic sites: Lung Bone Liver lymph nodes Other (%)
Bracarda (2015)													
Medical records	France	Retrospective cohort	Trad. 4/2	50 mg (50 mg)	NR	NR	Median: 59 (28–86)	77.7	73.9 25.1 NR 0.9	NR	34.1 60.7 5.2	86.7 10.4 2.9	65.4 25.6 19.4 NR 3.8
Bracarda (2015)													
–	–	–	Trans. 2/1	50 mg (50 mg)	NR	NR	Median: 62 (25–82)	71.6	73.1 25 NR 1.9	NR	42.3 52.4 5.3	94.7 3.4 1.9	59.6 21.6 15.4 NR 3.8
Bracarda (2015)													
–	–	–	Alt. 2/1	50 mg (50 mg)	NR	NR	Median: 61 (32–82)	63.4	58.5 36.6 NR 4.9	NR	24.4 65.8 9.8	87.8 7.3 4.9	65.9 26.8 26.8 NR 9.8
Ezz (2017)													
Medical records	Egypt	Retrospective cohort	Trad. 4/2	NR	NR	Median: 30 (range: 29.5 [as reported])	Median: 49 (25–76)	66.7	53.3 30 NA 16.7	26.7 63.3 10	NR	76.7 6.7 16.6	80 20 6.7 33.3 56.7
Ezz (2017)													
–	–	–	Alt. 2/1	NR	NR	Median: 30 (range: 30 [as reported])	Median: 49.5 (21–71)	57.5	34.6 26.9 NA 38.5	30.8 53.8 15.4	NR	88.5 3.8 7.7	76.9 30.8 19.2 23.1 61.5
Kondo (2014)													
Medical records	Tokyo	Retrospective cohort	Trad. 4/2	50 mg; 7 pts (32%) [†]	Mean: 9.2 months (range: 1.5–39)	Mean: 13.3 (SD: 10.1; range: 1.5–39.1)	Mean: 62.7 (31–78)	68	68 27 NR 5	0 78 22	NR	91 9 NA	73 9 14 27 NR
Kondo (2014)													
–	–	–	Tran. 2/1	50 mg; 9 pts (35%) [‡]	Mean: 9.7 months (range: 1.5–32)	Mean: 11.9 (SD: 8.1; range: 2.6–31.6)	Mean: 64.6 (31–79)	77	73 15 NR 12	27 58 15	NR	96 4 NA	69 15 12 27 NR

[†] 37.5 mg; 14 pts (64%); 25 mg; 1 pt (4%). The dose was increased by 12.5 mg/day until the authors found the highest tolerable dose for patients but did not exceed 50 mg/day.

[‡] 37.5 mg; 14 pts (54%); 25 mg; 3 pts (11%). The dose was increased by 12.5 mg/day until the authors found the highest tolerable dose for patients but did not exceed 50 mg/day.

[§] 16 patients (53%) were dose reduced after a median of eight weeks (range: 2–108) as follows: 15 patients: 37.5 mg; one patient: 25 mg.

alt: Alternative; ECOG: Eastern Cooperative Oncology Group; fav: Favourable; HRG: Heng Risk Group; intermed: Intermediate; ITT: Intention-to-treat; maint: Maintenance; MSKCC: Memorial Sloan Kettering Cancer Center; mo: Month; NA: Not applicable; NR: Not reported; pt: Patient; SD: Standard deviation; trad: Traditional, tran: Transitional, unfav: Unfavourable; yr: Year.

Table 1. Overview of trials included in the network meta-analysis (cont.).

Data source Registry Trial name	Country	Study design	Dosing schedule	Initial (maint.) dose	Treatment duration	Follow-up time (months)	Age (range)	Male (%)	ECOG status (0/1/2/≥2; %)	MSKCC status: Fav. Intermed. Unfav. (%)	HRG: Fav. Intermed. Unfav. (%)	Histology clear cell/ Papillary Other (%)	Metastatic sites: Lung Bone Liver lymph nodes Other (%)
Lee (2015)													
RESTORE trial	Korea	Multicenter, randomized, open-label, Phase II trial	Trad. 4/2 (ITT)	50 mg (NR)	NR	Median: 30	Median: 60 (32–76)	89	NR	19 53 28	11 56 33	100 NA NA	72 31 17 NR NR
Lee (2015)													
–	–		Trad. 4/2 (as treated)	50 mg (NR)	NR	Median: 30	Median: NR	NR	NR	NR	NR	100 NA NA	NR
Lee (2015)													
–	–	–	Tran. 2/1 (as treated)	50 mg (NR)	NR	Median: 30	Median: NR	87.5	50 50 NR NR	37.5 62.5 NA	NR	100 NA NA	NR
Lee (2015)													
–	–	–	Alt. 2/1 (ITT)	50 mg (NR)	NR	Median: 30	Median: 57 (41–79)	79	NR	18 50 32	13 45 42	100 NA NA	76 29 11 NR NR
Miyake (2015)													
Medical records	Japan	Retrospective cohort	Trad. 4/2	NR	Median: 3.4 months (range 1.3–19.7)	NR	Median: 61.5 (41–80)	80	NR	26.7 53.3 20	NR	91.1 NA 8.9	64.4 28.9 13.3 31.1 8.9
Miyake (2015)													
–	–	–	Tran. 2/1	NR	NR	NR	Median: 61.5 (41–80)	80	NR	26.7 53.3 20	NR	91.1 NA 8.9	64.4 28.9 13.3 31.1 8.9
Najjar (2014)													
Medical records	US	Retrospective cohort	Trad. 4/2	50 mg (50 mg) [§]	Median: 12.6 mo. (range: 1.2 mo. to 5.1 yr.)	NR	Median 60 (36–78)	73	NR	NR	23 53 23	81 NA 19	67 20 20 37 50

† 37.5 mg; 14 pts (64%); 25 mg; 1 pt (4%). The dose was increased by 12.5 mg/day until the authors found the highest tolerable dose for patients but did not exceed 50 mg/day.
‡ 37.5 mg; 14 pts (64%); 25 mg; 3 pts (11%). The dose was increased by 12.5 mg/day until the authors found the highest tolerable dose for patients but did not exceed 50 mg/day.
§ 16 patients (53%) were dose reduced after a median of eight weeks (range: 2–108) as follows: 15 patients: 37.5 mg; one patient: 25 mg.
alt: Alternative; ECOG: Eastern Cooperative Oncology Group; fav: Favourable; HRG: Heng Risk Group; intermed: Intermediate; ITT: Intention-to-treat; maint: Maintenance; MSKCC: Memorial Sloan Kettering Cancer Center; mo: Month; NA: Not applicable; NR: Not reported; pt: Patient; SD: Standard deviation; Trad: Traditional; tran: Transitional; unfav: Unfavourable; yr: Year.

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Najjar (2014)													
-	-	-	Tran. 2/1	50 mg (50 mg: 14 pts 37.5 mg: 15 pts 25 mg: 1 pt)	Median: 11.9 months (range: 0.9 to 73.3 mo.)	NR	Median: 60 (36-78)	73	NR	NR	23 53 23	81 NA 19	67 20 20 37 50
Neri (2013)													
NR	NR	Non- randomized Phase II trial	Tran. 2/1	50 mg (NR)	NR	NR	Median: NR	NR	NR	NR	NR	NR	NR
Neri (2013)													
-	-	-	Alt. 2/1	50 mg (NR)	NR	NR	Median: NR	NR	NR	NR	NR	NR	NR
Pan (2015)													
Medical records	China	Retrospective cohort	Trad. 4/2	50 mg (50 mg)	NR	Median: 20.4 (range: 15.6-32.4)	Median: 62 (41-76)	56	70 20 NA 10	20 56 24	NR	80 NA 20	70 20 16 34 6
Pan (2015)													
-	-	-	Tran. 2/1	50 mg (50 mg)	NR	Median: 20.4 (range: 15.6-32.4)	Median: 64 (40-74)	54	61.5 27.9 NA 11.5	23.1 38.5 38.5	NR	84.6 NA 15.4	61.5 23.1 15.4 38.5 0
Pan (2015)													
-	-	-	Alt. 2/1	50 mg (50 mg)	NR	Median: 20.4 (range: 15.6-32.4)	Median: 66 (45-80)	59	75 15.6 NA 9.4	18.8 59.4 21.9	NR	84.4 NA 15.6	68.8 18.8 15.6 31.3 3.1
Suo, 2017													
Pharmacy database	Canada	Retrospective cohort	Trad. 4/2	50 mg (NR)	NR	NR	Mean (SD): 60.8 (10.9)	78	34.7 38.8 NA 22	NR	13.6 45.8 40.7	83.1 NA 16.9	NR NR NR NR 8.5

† 37.5 mg: 14 pts (64%); 25 mg: 1 pt (4%). The dose was increased by 12.5 mg/day until the authors found the highest tolerable dose for patients but did not exceed 50 mg/day.

‡ 37.5 mg: 14 pts (54%); 25 mg: 3 pts (11%). The dose was increased by 12.5 mg/day until the authors found the highest tolerable dose for patients but did not exceed 50 mg/day.

§ 16 patients (53%) were dose reduced after a median of eight weeks (range: 2-108) as follows: 15 patients: 37.5 mg; one patient: 25 mg.

alt: Alternative; ECOG: Eastern Cooperative Oncology Group; fav: Favourable; HRG: Heng Risk Group; intermed: Intermediate; ITT: Intention-to-treat; maint: Maintenance; MSKCC: Memorial Sloan Kettering Cancer Center; mo: Month; NA: Not applicable; NR: Not reported; pt: Patient; SD: Standard deviation; trad: Traditional; tran: Transitional; unfav: Unfavourable; yr: Year.

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Suo, 2017													
-	-	-	Trad. 4/2	37.5 mg, 25.0 mg, or 12.5 mg (NR)	NR	NR	Mean (SD): 65.4 (10.3)	70	48.1 34.6 NA 15	NR 22.2 63.3 16.7	22.2 63.3 16.7	90 NA 10	NR NR NR NR 6.7
Suo, 2017													
-	-	-	Alt: 2/1	50 mg (NR)	NR	NR	Mean (SD): 62.3 (6.9)	77.8	42.9 42.9 NA 11.1	NR 22.2 33.3 44.4	22.2 33.3 44.4	100 NA 0	NR NR NR NR 0
Suo, 2017													
-	-	-	Alt: 2/1	37.5 mg, 25.0 mg, or 12.5 mg (NR)	NR	NR	Mean (SD): 66.7 (11.0)	72	18.2 50 NA 28	NR 20 48 32	20 48 32	84 NA 16	NR NR NR NR 8

† 37.5 mg: 14 pts (64%); 25 mg: 1 pt (4%). The dose was increased by 12.5 mg/day until the authors found the highest tolerable dose for patients but did not exceed 50 mg/day.

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Figure 1. Network diagram.

2/1: Alternative 2/1 schedule; 4/2: Classical 4/2 schedule; t2/1: Transitional schedule (4/2 switch to 2/1).

schedules for CR, ORR, PR, PD or SD. The MA results for OS and PFS are presented in Table 2. MA results for response outcomes appear in Table 3.

Safety

Patients treated with the classical 4/2 schedule had substantially higher odds of having grade 3–4 hand-foot syndrome compared with those treated with the alternative 2/1 schedule (OR: 0.33 [95% CrI: 0.12–0.79]). Although the classical 4/2 schedule was associated with numerically higher odds of fatigue, neutropenia and thrombocytopenia, no statistical differences between these dosing schedules were observed for any other grade 3–4 events. The results for the alternative 2/1 schedule compared with the classical 4/2 schedule with regards to anemia and diarrhea were similar (anemia OR: 0.97 [95% CrI: 0.33–2.89] and diarrhea OR: 0.99 [95% CrI: 0.26–3.7]). The MA results for safety outcomes are presented in Table 4 and Table 5.

MA results: transitional 2/1 versus classical 4/2 schedule

Effectiveness

Treatment with the transitional 2/1 schedule showed a trend for prolonging PFS compared with treatment with the classical 4/2 schedule (HR: 0.4 [95% CrI: 0.14–1.12]). The network for PFS included only three studies, two of which reported conflicting directionality of PFS outcomes (PFS and TTP). The sensitivity analysis that excluded RCT data further weakened the base-case findings as demonstrated through wider confidence intervals. No statistical differences were observed between dosing schedules for CR, ORR, PR, PD or SD. However, there was a decreased trend for patients who were treated with the transitional 2/1 schedule to achieve CR (OR: 1.29 [95% CrI: 0.23–7.36]), and an increased trend of achieving PR (OR: 0.74 [95% CrI: 0.17–3.25]) and ORR (OR: 0.79 [95% CrI: 0.25–2.53]) compared with those treated with the classical 4/2 schedule.

Safety

Patients treated with the transitional 2/1 schedule, compared with the classical 4/2 schedule, had statistically lower odds of having grade 3–4 diarrhea (OR: 0.32 [95% CrI: 0.12–0.87]), fatigue (OR: 0.34 [95% CrI: 0.15–0.75]) and hand-foot syndrome (OR: 0.37 [95% CrI: 0.18–0.75]). There were no statistical differences observed between these dosing schedules for any other grade 3–4 AEs. However, patients on the transitional 2/1 schedule had numerically lower odds of having leukopenia (OR: 0.72 [95% CrI: 0.13–4.11]), nausea (OR: 0.4 [95% CrI: 0.07–2.1]) and

Table 2. Summary of pairwise meta-analysis and network meta-analysis effectiveness results: survival outcomes.

Outcome	PFS						OS				
	Base case (all studies)		Sensitivity analyses (without Lee, 2015)		Sensitivity analyses (with ITT from Lee, 2015)		Base case (all studies)		Sensitivity analyses (without Lee, 2015)	Sensitivity analyses (with ITT from Lee, 2015)	
Model	FE	RE	FE	RE	FE	RE	FE	RE	FE	FE	RE
HR (95% CrI)											
Comparisons											
Alternative 2/1 vs classical 4/2 (NMA)	0.75 (0.6–0.94) [†]	0.74 (0.45–1.21)	0.81 (0.63–1.03)	0.79 (0.45–1.4)	0.8 (0.64–1)	0.8 (0.61–1.03)	0.98 (0.75–1.29)	0.97 (0.62–1.5)	0.94 (0.69–1.28)	0.98 (0.75–1.29)	0.97 (0.62–1.48)
Alternative 2/1 vs classical 4/2 (pairwise MA)	0.75 (0.6–0.94) [†]	0.75 (0.6–0.94) [†]	0.81 (0.64–1.03)	0.81 (0.64–1.03)	0.8 (0.64–1)	0.8 (0.64–1)	0.98 (0.75–1.29)	0.98 (0.74–1.3)	0.94 (0.69–1.27)	0.98 (0.75–1.29)	0.98 (0.74–1.3)
Transitional 2/1 vs classical 4/2 (NMA)	0.28 (0.24–0.33) [†]	0.41 (0.21–0.84) [†]	0.29 (0.24–0.35) [†]	0.49 (0.22–1.19)	NA	NA	0.33 (0.25–0.43) [†]	0.33 (0.15–0.7) [†]	0.32 (0.25–0.42) [†]	NA	NA
Transitional 2/1 vs classical 4/2 (pairwise MA)	0.33 (0.26–0.42) [†]	0.4 (0.14–1.12)	0.34 (0.27–0.43)	0.53 (0.13–2.22)	NA	NA	NA	NA	NA	NA	NA
Sqrt(tau)	NA	0.5303	NA	0.5701	NA	0.1064	NA	0.2457	NA	NA	0.2438
DIC	33.39	10.09	30.95	7.117	-0.3935	1.481	3.412	4.541	3.648	3.876	4.971

[†]Statistically significant results.

The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset that has the same structure as that currently observed. Tau is the common heterogeneity parameter, which indicates the variance of the underlying distribution.

CrI: Credible interval; DIC: Deviance information criterion; FE: Fixed-effects; HR: Hazard ratio; ITT: Intention-to-treat; MA: Meta-analysis; N/A: Not applicable; NMA: Network meta-analysis; OR: Odds ratio; OS: Overall survival; PFS: Progression-free survival; RE: Random-effects.

Table 3. Summary of pairwise meta-analysis and network meta-analysis effectiveness results: response outcomes.

Outcome	Objective response		Complete response		Partial response		Progressive disease		Stable disease	
	Base case									
Model	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE
Comparisons	OR (95% CrI)									
Alternative 2/1 vs classical 4/2 (NMA)	1.22 (0.63–2.32)	1.17 (0.46–2.8)	0.74 (0.14–3.35)	0.72 (0.11–3.73)	1.33 (0.66–2.64)	1.24 (0.44–3.16)	0.44 (0.2–0.93) [†]	2.54 (1.2–5.5)	2.76 (0.89–9.39)	NA
Alternative 2/1 vs classical 4/2 (pairwise MA)	1.31 (0.68–2.53)	1.31 (0.68–2.53)	0.79 (0.19–3.25)	0.79 (0.19–3.25)	1.47 (0.72–3)	1.47 (0.72–3)	0.51 (0.23–1.12)	2.12 (0.98–4.6)	2.4 (0.67–8.58)	NA
Transitional 2/1 vs classical 4/2 (NMA)	0.79 (0.32–1.86)	0.81 (0.26–2.46)	1.03 (0.19–5.27)	1.01 (0.15–6.42)	0.72 (0.26–1.88)	0.77 (0.23–2.71)	0.57 (0.25–1.29)	2.07 (0.96–4.42)	2.14 (0.67–7.22)	NA
Transitional 2/1 vs classical 4/2 (pairwise MA)	0.78 (0.33–1.83)	0.79 (0.25–2.53)	1.29 (0.23–7.36)	1.29 ([0.23–7.36)	0.7 (0.27–1.77)	0.74 (0.17–3.25)	0.66 (0.28–1.52)	1.81 (0.81–4.04)	1.95 (0.45–8.5)	NA
Sqrt(tau)	NA	0.4266	NA	0.4657	NA	0.4924	N/A	NA	0.5932	NA
DIC	47.24	47.8	32.22	32.62	46.91	46.78	37.91	40.51	39.11	NA

[†]Statistically significant results.

The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset that has the same structure as that currently observed. Tau is the common heterogeneity parameter, which indicates the variance of the underlying distribution.

CrI: Credible interval; DIC: Deviance information criterion; FE: Fixed-effects; MA: Meta-analysis; NA: Not applicable; NMA: Network meta-analysis; OR: Odds ratio; RE: Random-effects.

Table 4. Summary of pairwise meta-analysis and network meta-analysis results: safety outcomes (anemia, diarrhea, fatigue, hand and foot syndrome).

Outcome	Anemia		Diarrhea		Fatigue		Hand and foot syndrome		
					Base case				
Model	FE	RE1	FE	RE1	FE	RE1	FE	RE1	RE0.5
Comparisons	OR (95% CrI)								
Alternative 2/1 vs classical 4/2 (NMA)	0.86 (0.29–2.4)	0.82 (0.24–2.63)	0.95 (0.35–2.3)	0.89 (0.24–2.89)	0.23 (0.06–0.64) [†]	0.24 (0.06–0.76) [†]	0.36 (0.16–0.74) [†]	0.33 (0.12–0.79) [†]	0.35 (0.15–0.77) [†]
Alternative 2/1 vs classical 4/2 (pairwise MA)	0.97 (0.33–2.89)	0.97 (0.33–2.89)	1.27 (0.52–3.07)	0.99 (0.26–3.7)	0.51 (0.18–1.41)	0.47 (0.14–1.57)	0.44 (0.21–0.92) [†]	0.44 (0.21–0.92) [†]	0.44 (0.21–0.92) [†]
Transitional 2/1 vs classical 4/2 (NMA)	1.05 (0.36–3.05)	1.05 (0.29–3.61)	0.19 (0.06–0.47) [†]	0.2 (0.06–0.6) [†]	0.31 (0.14–0.64) [†]	0.32 (0.12–0.8) [†]	0.29 (0.14–0.56) [†]	0.26 (0.1–0.59) [†]	0.27 (0.12–0.57) [†]
Transitional 2/1 vs classical 4/2 (pairwise MA)	0.92 (0.27–3.12)	0.92 (0.27–3.12)	0.32 (0.12–0.87) [†]	0.32 (0.12–0.87) [†]	0.34 (0.15–0.75) [†]	0.34 (0.15–0.75) [†]	0.37 (0.18–0.75) [†]	0.37 (0.18–0.75) [†]	0.37 (0.18–0.75) [†]
Sqrt(tau)	NA	0.4352	NA	0.6483	NA	0.5255	NA	0.4377	0.2566
DIC	52.18	52.77	62.21	60.04	79.47	78.88	71.66	72.24	71.69

[†]Statistically significant results.

The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset that has the same structure as that currently observed. Tau is the common heterogeneity parameter, which indicates the variance of the underlying distribution.

CrI: Credible interval; DIC: Deviance information criterion; FE: Fixed-effects; MA: Meta-analysis; NA: Not applicable; NMA: Network meta-analysis; OR: Odds ratio; RE: Random-effect.

Table 5. Summary of pairwise meta-analysis and network meta-analysis results: safety outcomes (leukopenia, nausea, neutropenia, thrombocytopenia).

Outcome	Leukopenia		Nausea		Neutropenia		Thrombocytopenia	
					Base Case			
Model	FE	RE	FE	RE	FE	RE	FE	RE
Comparisons	OR (95% CrI)							
Alternative 2/1 vs classical 4/2 (NMA)	0.94 (0.02–38.94)	0.94 (0.02–39.57)	1.41 (0.04–12.57)	1.36 (0.03–16.3)	0.49 (0.2–1.12)	0.51 (0.18–1.44)	0.18 (0.03–0.61)	0.15 (0.02–0.66)
Alternative 2/1 vs classical 4/2 (pairwise MA)	NA	NA	NA	NA	0.44 (0.18–1.08)	0.44 (0.18–1.08)	0.36 (0.11–1.22)	0.36 (0.11–1.22)
Transitional 2/1 vs classical 4/2 (NMA)	0.68 (0.26–1.72)	0.71 (0.2–2.5)	0.35 (0.05–1.77)	0.35 (0.04–2.13)	1.18 (0.49–2.82)	1.17 (0.38–3.47)	0.47 (0.26–0.83) [†]	0.46 (0.19–1.01)
Transitional 2/1 vs classical 4/2 (pairwise MA)	0.6 (0.21–1.72)	0.72 (0.13–4.11)	0.4 (0.07–2.1)	0.4 (0.07–2.1)	1.36 (0.53–3.49)	1.36 (0.53–3.49)	0.54 (0.3–0.97) [†]	0.5 (0.2–1.25)
Sqrt(tau)	NA	0.6312	NA	0.4751	NA	0.3915	NA	0.5547
DIC	38.6	37.05	19.53	19.92	47.94	48.83	64.17	63.22

[†]Statistically significant results.

The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset that has the same structure as that currently observed. Tau is the common heterogeneity parameter, which indicates the variance of the underlying distribution.

CrI: Credible interval; DIC: Deviance information criterion; FE: Fixed-effects; MA: Meta-analysis; NA: Not applicable; NMA: Network meta-analysis; OR: Odds ratio; RE: Random-effects.

thrombocytopenia (OR: 0.5 [95% CrI: 0.2–1.25]), but numerically higher odds for neutropenia (OR: 1.36 [95% CrI: 0.53–3.49]) compared with the classical 4/2 schedule.

MA results: heterogeneity diagnostics

While no statistical heterogeneity was observed during the comparisons of the alternative 2/1 schedule to the classical 4/2 schedule, considerable statistical heterogeneity was found in the direct evidence related to the transitional 2/1 schedule when data were compared using classical pairwise MA for PFS ($I^2 = 95.3\%$). This result was based on two studies, and it could not be adjusted for the model due to a lack of individual patient-level data. This limits the generalizability of the meta-analytic average derived from the analysis.

*Exploratory NMA results**Effectiveness*

The alternative 2/1 and transitional 2/1 schedules demonstrated more favorable results compared with the classical 4/2 schedule across all effectiveness outcomes. While there were no clear statistical differences between the regimens with regard to PFS, there was a tendency for the alternative 2/1 and transitional 2/1 schedules to prolong this outcome compared with the classical 4/2 schedule. This trend continued for the alternative 2/1 schedule in OS. The transitional 2/1 schedule had a statistical advantage over the classical 4/2 schedule. However, this finding should be interpreted with caution as it is based on the data from a single study.

Similar trends to those seen in the pairwise MA were observed in the NMA comparisons for CR, ORR, PD and SD for each treatment schedule comparison, with all having no statistical advantage. With regard to PD, a statistical advantage in prevention of disease progression was found for the alternative 2/1 schedule over the classical 4/2 schedule. This finding was not statistically different within the pairwise MA; it should be interpreted with caution as the network was composed of only two studies.

Safety

No statistical differences between the dosing schedules were found for the NMA safety results, and rates of individual grade 3–4 AEs were variable across comparisons. Treatment with the classical 4/2 schedule vs the alternative 2/1 schedule was associated with numerically higher odds of anemia, diarrhea and neutropenia. The odds of leukopenia, nausea and thrombocytopenia associated with the classical 4/2 schedule were numerically higher relative to the transitional 2/1 schedule.

Potential Sources of bias & their likely impact on the interpretation of the results

Two broad groups of bias were identified among the included studies, and it is important to consider the impact of these while interpreting the results of the classical MA and the NMA. One inherent feature of all the studies' design – except one, the RESTORE trial [26] – was selection bias due to the uncontrolled, nonrandomized methods used to select the included sample. Although no formal risk-of-bias assessment was conducted for the included studies, those individual-study results reported for the transitional 2/1 dosing schedule involved some form of patient channeling, which led to the very different results observed for patients who received that treatment. Two of the included studies [26,28] also potentially had some degree of 'immortal time bias' [36], given that those patients who transitioned would have been treated for longer, which could have made their results more favorable from the beginning of treatment.

Discussion

There is strong clinical evidence that demonstrates that sunitinib is effective in patients with mRCC when delivered at the conventional dose of 50 mg daily with the classical schedule (4/2: 4 weeks yes and 2 weeks not). Although generally associated with acceptable, and manageable toxicity, sunitinib frequently results in AEs that could potentially lead to early treatment discontinuation. Recent literature suggests there may be alternative dosing schedules that maintain the established efficacy profile seen with the classical 4/2 schedule while also minimizing toxicity [17–20,26,28,31,35].

Schedule changes with the classical schedule may be considered before lowering the dose to retain the optimal level of exposure to sunitinib. However, there is currently some doubts within the existing literature on which schedule may be optimal with regards to safety and effectiveness for the treatment of mRCC. An SLR and MA were conducted to compare two alternative sunitinib dosing schedules, the alternative 2/1 and the transitional 2/1 schedule, to the classical 4/2 schedule.

The comparison of sunitinib dosing schedules within the existing literature is limited and direct comparisons are not available, especially for the transitional 2/1 schedule. A systematic review summarizing sunitinib dosing

schedules was conducted in 2014 [37]. Yet, the current study includes updated literature and also has meta-analyzed the outcomes reported in included relevant studies. Therefore, it is a comprehensive overview of evidence and is reflective of current real-world clinical practice. It is the first peer-reviewed study to our knowledge to systematically evaluate the comparative safety and effectiveness of sunitinib dosing schedules in mRCC.

A pairwise MA found the alternative 2/1 and transitional 2/1 schedules to numerically prolong PFS when compared with the classical 4/2 schedule. Nevertheless, only the alternative 2/1 comparison had a statistical advantage, and this difference was not evident in sensitivity analyses.

The PFS estimate generated for the NMA compared the transitional 2/1 to the classical 4/2 schedule indicated that the former schedule has a statistical advantage in extending PFS compared with the latter; however, the direct comparison did not find any such statistical advantage. The divergence may have resulted from the lack of sufficient power to detect differences due to the sample size disparity in the studies by Bracarda *et al.* [28] and Pan *et al.* [31] (N = 460 and N = 108, respectively). Nonetheless, we were unable to fully account for the inconsistencies observed for these two studies due to a lack of publicly available data.

OS was also numerically prolonged for the alternative 2/1 and transitional 2/1 schedules compared with the classical 4/2 schedule. Only the comparison with transitional 2/1 was statistically different for OS, but this result should be viewed with caution as it is based on data from only one study [28]. Within this study, patients in the transitional 2/1 arm were treated for a longer duration than the classical 4/2 patients, which indicated that they likely would have lived longer irrespective of the effectiveness of the former schedule.

Hypertension and thyroid dysfunction was captured in most of the included studies but were however not analyzed in this analysis as the safety outcomes for which MA and NMA were conducted were considered more clinically relevant to sunitinib treatment. Among safety outcomes, the most robust data within the MA related to the occurrence of hand-foot syndrome. The alternative 2/1 and transitional 2/1 schedules demonstrated statistically lower odds of the disease than the classical 4/2 schedule in both pairwise MA and NMA results. Sunitinib has also been found to have a better outcome in randomized settings in this safety outcome even in comparison to other VEGFR inhibitors, such as cabozantinib [38]. Future research should compare the impact of VEGFR inhibitors on this and other safety outcomes. Further advantages were seen with the transitional 2/1 schedule in terms of fatigue and diarrhea.

A key strength of the MAs in our study was the generation of summary statistics and assessment of statistical heterogeneity using well-established methods. While the estimates for most outcomes did not show clear statistical advantages, these findings may be important in clinical practice.

Our analysis has some limitations. Of the 11 studies included in the review, only one was an RCT, and the remaining ten were observational in design. An MA of clinical data derived from an observational design is uncommon and challenging in terms of bias and in finding consistency in reported outcomes and definitions. Some of the treatment arms included small sample sizes, which raised the possibility that the studies may have had insufficient power to detect differences in the outcomes measured. In addition, of the two potentially relevant prospectively conducted studies identified by the review, only the RESTORE trial conducted by Lee *et al.* [26] provided comparative data, while the other study by Jonasch *et al.* [39] was excluded from the review for lack of a comparative arm.

There were several limitations in the statistical analysis of PFS outcomes within the study set. First, PFS data were not available in the RCT publication, so TTP data were used as a proxy. While PFS is preferred over TTP in oncology, it appears they could be used interchangeably on the assumption that deaths occurred in studies reported in the TTP outcome are not related to the cancer [40]. We were, however, unable to determine whether this was the case for the RCT [26] in reporting this outcome because of our lack of access to patient-level data. Further, considerable statistical heterogeneity ($I^2 = 95.3\%$) was found in the direct evidence related to the transitional 2/1 schedule, but this result was based on only two studies that had conflicting outcomes. Selection bias, differences in sample sizes and the possible impact of confounding resulting from the use of observational data are likely explanations for this difference in observed effects for the same intervention across the studies.

The inclusion of arms for the transitional 2/1 schedule in this review may have also opened the analysis to additional immortal time bias. However, an examination of the studies reporting data on time to switching from the classical 4/2 schedule to the alternative 2/1 schedule found that the switch occurs after approximately 3 months [28,31]. It is therefore less likely that immortal time bias truly existed in the studies evaluating transitional 2/1 schedules.

Further, there was a lack of adjusted observational data within the study set, and that prevented potential confounding variables from being identified. The analysis could have benefited from conducting propensity score matching of included studies for balancing comparison arms with respect to known and unknown prognostic factors, but this is only achievable with patient-level data, to which we did not have access for any of the studies. Two publications, however, reported numerical data that had been adjusted for confounding factors using Cox proportional hazards regression analysis [29,35]. There was also a limited number of studies evaluating or providing data for comparisons. This prevented us from estimating a random-effects variance. Inferences from these outcomes are based on results of the fixed-effects models, which do not take the heterogeneity among studies into account.

The SURF study (ClinicalTrials.gov: NCT02689167), a randomized, Phase II trial, will further explore the benefits of using a transitional sunitinib schedule versus applying dose reduction. It is an ongoing investigation of the safety and efficacy of changing dosing schedules versus decreasing the dose of sunitinib in patients with mRCC experiencing toxicity on the 4/2 schedule. The primary end point of the study, which is expected to enroll 248 patients, is to determine the duration of treatment in both arms [41].

Conclusion

Evidence from this systematic review and MA indicates the benefits of sunitinib dosing schedules on clinical outcomes among patients with mRCC. The results show that the alternative 2/1 and transitional 2/1 schedules were generally better tolerated and more effective than the classical 4/2 schedule. While the estimates for most outcomes were not statistically significant, favorable trends were observed and therefore, the findings from these MAs could be useful in determining which schedules patients can potentially be offered in real-world clinical practice. However, these results should be interpreted with caution due to the heterogeneity between the studies and some lack of consistency in reporting of outcomes.

The trends observed in the present study favoring alternative and transitional sunitinib schedules are in accordance with routine real-world clinical practice. Guidelines recommend treating mRCC with the 50 mg daily classical 4/2 schedule. Patients who cannot tolerate sunitinib at the classical 4/2 schedule may be moved to the 2/1 schedule to retain the daily 50 mg dosing when possible. Thus, our findings are aligned with current real-world practice. Despite that this research synthesis provides the best available evidence to date on the subject, the evidence base for studies including the transitional 2/1 schedule is weak and sparse. Future prospective trials or real-world evidence evaluating this schedule will be helpful in determining the relevance of this approach for treating patients with mRCC.

Future perspective

Providing patient-centred care using a personalized approach is playing a key role in the management of mRCC and oncology in general. This study shows that the evidence to support the use of a treatment in real world clinical practice may evolve over time to provide better outcomes and improved tolerability.

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Executive Summary

Background

- Sunitinib, a tyrosine kinase inhibitor (TKI), is a first-line treatment that has demonstrated improved outcomes in metastatic renal cell carcinoma (mRCC).
- The optimal dosing schedule to maintain its effectiveness – while reducing toxicity – remains an important clinical question.
- The objective of this review was to compare the effectiveness and safety of different sunitinib dosing schedules for mRCC treatment.

Methods

- A systematic review and meta-analysis of randomized controlled trials and longitudinal observational studies, published in English, were conducted to assess clinical results of the classical 4/2, alternative 2/1 and transitional 2/1 sunitinib schedules for treating patients with mRCC.
- Bayesian mixed treatment comparison analyses and network meta-analyses were performed to compare the relative treatment effects of schedules on overall survival (OS), progression-free survival (PFS), response and grade 3–4 adverse events (AEs).

Results

- Of the 692 records reviewed, 11 primary studies (one randomized trial and ten observational studies) were included and nine were considered eligible for the meta-analysis.
- Treatment with the alternative 2/1 schedule reduced the risk of disease progression or death by 25% compared with the classical 4/2 schedule (hazard ratio [HR]: 0.75 [95% credible interval (CrI): 0.60, 0.94]).
- A numerical but not 'statistical' benefit in PFS was observed with the transitional compared with the classical schedule.
- The odds of fatigue and diarrhea were lower for the transitional 2/1 schedule compared with the classical 4/2 schedule (odds ratio [OR]: 0.32 [95% CrI: 0.12–0.87]).
- The alternative 2/1 (OR: 0.44 [95% CrI: 0.21–0.92]) and transitional 2/1 (OR: 0.37 [95% CrI: 0.18–0.75]) schedules demonstrated statistically lower odds of hand and foot syndrome than the classical 4/2 schedule.

Conclusion

- Benefits of alternative sunitinib schedules on clinical outcomes among patients with mRCC were demonstrated.
- The alternative 2/1 and transitional 2/1 schedules appeared generally better tolerated and more effective than the classical 4/2 schedule.

Data sharing statement

Upon request, and subject to certain criteria, conditions and exceptions (see www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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