National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG111 Sunitinib | Advice Document v1.0 | January 2024

Sunitinib as second line treatment of poor or intermediate risk advanced/metastatic renal cell carcinoma in patients who have received nivolumab in combination with ipilimumab as first line treatment[A].

NCMAG Decision | this on-label off-patent use is **supported**

This advice applies only in the context of the confidential pricing agreements in NHSScotland, upon which the decision was based, or confidential pricing agreements or list prices that are equivalent or lower.

[A] NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith SMC remit. For more detail on NCMAG remit please see our website.

Decision rationale

After consideration of all the available evidence regarding the clinical benefits and harms, the Council were satisfied with the clinical effectiveness case for sunitinib in the proposed population. After consideration of all relevant information under the Decision-making framework for value judgements the Council made a decision to support this use.

Governance Arrangements

Each NHS board must ensure all internal governance arrangements are completed before medicines are prescribed. The benefits and risks of the use of a medicine should be clearly stated and discussed with the patient to allow informed consent.

Proposal Details	
Proposers	NHSScotland Renal Cancer Clinicians
Medicine Name	Sunitinib
Cancer type	Renal cell carcinoma
Proposed off-patent and on-label indication	Second line treatment of poor or intermediate risk advanced/metastatic renal cell carcinoma in patients who have received ipilimumab in combination with nivolumab as first line treatment.
Medicine Details	Form: Capsules

	Dose: 50 mg taken orally once daily, for 4 consecutive weeks, followed by a 2-week rest period (Schedule 4/2) to comprise a complete cycle of 6 weeks.[1] Treatment is continued until disease progression or unacceptable toxicity.
Treatment Marketing Authorisation	Sunitinib is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.[1]
Advice eligibility criteria	Performance Status 0 or 1

1. Current Management Context

Renal Cell Carcinoma incidence, prognosis, and symptoms

Renal cell carcinoma (RCC) is a type of cancer originating in the lining of the proximal tubules within the kidney's nephrons. It constitutes approximately 80% of all kidney cancers. Renal cell carcinomas are classified by cell type; clear cell RCC (ccRCC) represents 80% of RCC cases, while papillary and chromophobe variants make up most of the remaining 20%.[2] Kidney cancer was the eighth most common cancer in Scotland, with 994 cases diagnosed in 2020, of which 20% are diagnosed at the metastatic stage. Incidence is higher amongst males compared to females.[3] The risk of kidney cancer increases with age and most commonly occurs between 65 and 75 years of age.[4]

The International Metastatic RCC Database Consortium (IMDC) risk score, which assesses six risk factors, is used to stratify advanced or metastatic RCC into favourable, intermediate, or poor prognostic categories. Patients with intermediate risk present with one or two risk factors initially, whereas those with poor risk exhibit three or more.[2]

Historically, median overall survival has ranged from 8 months in patients with poor risk to 4 years in those with a favourable IMDC risk score.[2] However, these estimates are considered conservative as they are based on data prior to the introduction of first-line immune checkpoint inhibitors (ICIs). Such therapies include ipilimumab plus nivolumab combination, and the combination of an ICI and vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKI), for example, pembrolizumab plus axitinib and nivolumab plus cabozantinib, which have significantly improved survival. Ipilimumab plus nivolumab is currently accessible for intermediate and poor risk patients in the first-line setting.

Symptoms of metastatic renal cell carcinoma include lower back pain, blood in the urine, weight loss, fatigue, fever and symptoms associated with areas of distant metastases.

National and international context for proposed on-label use

For ccRCC patients with poor or intermediate risk, second-line treatment options depend on the first-line therapy received. If an ICI was administered initially, recommended second-line treatment typically involves a VEGFR-TKI, although none have marketing authorisation for this specific indication. The European Association of Urology, the European Society of Medical Oncology and the National Comprehensive Cancer Network guidelines support a range of VEGFR-TKIs for second-line use, including sunitinib. For non-clear cell RCC, where supporting evidence is less robust, due to smaller patient cohorts, VEGFR-TKIs are also considered acceptable options.[5, 6, 2,7]

Although sunitinib is on-label for advanced/metastatic RCC (mRCC) in adults, a NICE Multiple Technology Assessment, undertaken before first line ICIs were available, and that is also applicable in Scotland, restricts its use to first-line treatment.[8] Other VEGFR-TKIs, such as cabozantinib and axitinib, are only accessible in Scotland after progression on another VEGFR-TKI or when given in combination with ICIs. Therefore, an unmet need exists in the second-line setting for patients

previously treated with ipilimumab plus nivolumab. As there are no routinely accessible treatment options access is dependent on individual patient treatment requests. Based on the lack of routine access to any cancer medicine for the proposed population, best supportive care is the relevant comparator for this review.

Pharmacology of sunitinib

Sunitinib is a multi-targeted kinase inhibitor and works by inhibiting the growth of blood vessels around tumours, thus potentially shrinking and halting tumour growth.[1]

2. Evidence Review Approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, major international health technology agencies, as well as a focused internet search. The search strategy comprised both Medical Subject Headings and keywords. The main search concepts were sunitinib, 'renal cell carcinoma', advanced, metastatic, and TKI. No filters were applied to limit the retrieval by study type. Titles and abstracts were screened by one reviewer with decisions crossed-checked with another reviewer. The included publications were critically appraised using the ROBINS-I tool (Risk Of Bias In Non-randomised Studies - of Interventions).[9]

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

Overview of evidence for use of sunitinib at second line

Six studies were identified as relevant to this proposal; five retrospective cohort studies and one phase II single arm study [10-15] (see Table 1). Two of the cohort studies (Barata et al and Shah et al) were excluded from this evidence review as the first-line therapy comprised of an ICI plus VEGFR-TKI combination which does not align to this proposal. [10, 12] Furthermore, the number of patients in these two studies receiving sunitinib as a second-line therapy was low. In the four included studies, the proportion of patients who received ipilimumab plus nivolumab at first-line ranged from between 14% to 100%. In two studies all patients had sunitinib at second-line, however, Grande et al did not report outcomes by the type of first-line ICI.[13, 15] For the remaining two studies, where only a proportion of patients received sunitinib at second-line, outcomes were reported for the sunitinib group by the type of first-line therapy. The Checkmate 214 study was a phase 3 trial which compared ipilimumab plus nivolumab with sunitinib for previously untreated ccRCC.[16] As this treatment comparison and the patient population are not directly relevant to this proposal the study was not included in the evidence section of this advice document. However, it is noted the Auvray et al study included patients that were enrolled in Checkmate 214 and subsequently treated with second-line VEGFR-TKI after progressing on first-line ipilimumab plus nivolumab treatment.

Table 1| Evidence matrix [10-15]

	First-line therapy ipilimumab plus nivolumab[a]		Second-line therapy Sunitinib	
Study, year Study design	**All study patients received Y/N (n)**	**Proportion of study patients (n)**	**All study patients received Y/N (n)**	**Proportion of study patients (n)**
Auvray et al, 2019 (n=33) Retrospective cohort	Y (33)	NA	N	51%(17)
Barata et al, 2018 (n=33) Retrospective cohort[d]	N	33%(11)	N	12%(4)[a]
Graham et al, 2021 (n=314) Retrospective cohort	N	81%(255)[b]	N	7%(17)
Grande et al, 2022 (n=23) Phase II, single-arm trial	N	14%(3)[c]	Y (23)[a]	NA
Shah et al, 2019 (n=70) Retrospective cohort[d]	N	47%(33)	N	9%(6)[a]
Wells et al, 2021 (n=102) Retrospective cohort	N	61%(62)	N	61% (62)

[a] Results not reported by type of first-line (1L) therapy. 1L therapies for these studies were as follows - Barata et al: atezolizumab plus bevacizumab (64%) or axitinib plus avelumab (3%); Shah et al: nivolumab or atezolizumab (17%), ipilimumab plus nivolumab (47%) and the remaining patients receiving either nivolumab plus bevacizumab or atezolizumab plus bevacizumab (36%); Grande et al; most common combinations were atezolizumab plus bevacizumab (29%), pembrolizumab monotherapy (14%) and ipilimumab plus nivolumab (14%).
[b] Nivolumab (alone or with ipilimumab)
[c] Based on 21 patients included in the analysis
[d] Study excluded from evidence review as the first-line therapy comprised of an ICI plus VEGFR-TKI combination

The evidence for the use of sunitinib at second line

Phase II single arm trial (the INMUNOSUN-SOGUG trial)

Grande et al conducted a multicentre, phase II, single-arm, open-label trial to investigate the efficacy of sunitinib as a second-line therapy for patients with mRCC who had progressed on first-line ipilimumab plus nivolumab, monotherapy, or ICI in combination with an anti-angiogenic therapy. The study included patients ≥18 years of age with a histologically confirmed diagnosis of ccmRCC. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2, adequate haematological and end-organ function, and measurable disease according to modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were included. Patients received sunitinib 50 mg once daily orally for 4 weeks followed by a 2-week rest period; this aligns with the proposed dosing regimen. Most patients received the following ICI-based combinations at first-line therapy; atezolizumab and bevacizumab (29%), pembrolizumab monotherapy (14%) and the combination of ipilimumab plus nivolumab (14%).

The primary outcome for the study was investigator-assessed overall response rate (ORR) (defined as the proportion of patients who had a confirmed best response of complete or partial response according to RECIST v1.1). The secondary outcomes were progression-free survival (PFS; defined as the time from beginning of treatment to evidence of progression or death), duration of response (defined as the time from the first occurrence of response to disease progression according to

RECIST v1.1 or death, whichever occurs first;) and overall survival (OS; defined as the time from beginning of treatment to death of any cause). On completion of treatment, patients were followed up every eight weeks.

Results from the INMUNOSUN-SOGUG trial

The median duration of sunitinib treatment was 5.1 months (interquartile range [IQR] 2.7 to 11.0 months). Median follow-up from the start of treatment with sunitinib was 15 months (IQR 7.6 to 24.1). The median age of patients was 67 years (IQR 59 to 73) with the majority male (86%) and with clear cell pathology (91%). The ECOG performance score was 1 in 94% of patients and 2 in 6% of patients. The proportion of patients with a favourable and intermediate prognosis as defined by the IMDC risk score was 6% and 94%, respectively. Results were not reported by type of first-line ICI received (Table 2).

Table 2 | Results for the INMUNOSUN-SOGUG trial

Outcome	Sunitinib (n=21[a])
Primary outcome: overall response rate (ORR) assessed by investigator per RECISTv1.1	
ORR, n (%)	4 (19)
Partial response, n (%)	4 (19)
Stable disease, n (%)	14 (67)
Secondary outcomes	
Median progression-free survival, months (95%CI)	5.6 (3.1 to 8.0)
Median overall survival, months (95%CI)	23.5 (6.3 to 40.7)
Duration of response, months (IQR)[b]	7.1 (4.2 to 12.0)

[a] Two out of 23 included patients were excluded from the analysis.
[b] Based on the four patients who showed an objective response.
Abbreviations: CI; confidence interval: IQR: interquartile range; ORR: overall response rate: RECIST; Response Evaluation Criteria in Solid Tumours.
Definitions: SD: Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. PR: Partial response: At least a 20% decrease in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative decrease of 20%, the sum must also demonstrate an absolute decrease of at least 5 mm.[17]

Non-comparative retrospective cohort studies

Three retrospective cohort studies comprise the remainder of the evidence for the use of sunitinib after first-line ICI among patients with mRCC.[10, 12, 15] One study reported data from a clinical trial, one study used IMDC data from seven centres and one study used data from a real-world evidence study. The median age of patients included in the studies ranged between 61 years to 63 years, and the majority of patients had clear cell histology and were classified as either having an IMDC risk group of intermediate or poor (see Table 3). The dosage schedule for sunitinib used in one of the studies aligns with the proposed dosage schedule[10]; the sunitinib dosing schedule was not reported in two of the studies.[12, 15]

Auvray et al reported on 33 patients with mRCC treated with second-line VEGFR-TKI after progressing on first-line ipilimumab plus nivolumab treatment in the setting of the Checkmate 214 clinical trial.[10 16] Outcomes measured included response, PFS, OS and safety. Results for the group

of patients treated with sunitinib at second-line (n=17) were reported separately apart for the response outcomes.

Graham et al reported on 314 patients with mRCC treated with second-line targeted therapy (VEGFR-TKIs or mammalian target of rapamycin inhibitors) following the discontinuation of ICI.[12] Outcomes measured included response, time to treatment discontinuation (TTD; defined as the time from initiation of sunitinib therapy to discontinuation for any reason) and overall survival. Results for the group of patients treated with sunitinib at second-line (n= 17) were reported separately.

Wells et al reported on 102 patients with mRCC treated with second-line sunitinib after first-line ICI.[15] At first-line, 62 (61%) patients received ipilimumab plus nivolumab, 27 (27%) received ICI plus VEGF therapy, and 13 (13%) received ICI monotherapy. Outcomes measured included response, time-to-treatment discontinuation, OS and safety. Results were reported by type of first-line therapy.

Common outcomes measured in the studies (response rates, PFS and OS) are presented in Tables 3 and 4.

Table 3| Response rates from of non-comparative studies[10, 12, 15]

Study name (n)	Participants (overall, unless stated otherwise)[a]	Response rates[b]		
		PR, n(%)	SD, n(%)	PD n(%)
Auvray et al France (n=33)[b]	Median age 61 Clear cell: not reported Prognostic group[c] – Favourable 15% – Intermediate 64% – Unfavourable 21%	12 (36)	13 (39)	5 (15)
Graham et al International (n=17)	Median age 62.8 Clear cell 91% Prognostic group – Favourable 11% – Intermediate 63% – Poor 26%	7 (54)	Not reported	Not reported
Wells et al International (n=62)	Median age 63 Clear cell 90% Prognostic group – Favourable 4% – Intermediate 56% – Poor 40%	11 (27)[d]	11 (27)	18 (45)

[a] Baseline characteristics are for the full population on initiation with VEGFR-TKI.
[b] Investigator-assessed according to RECIST v1.1. For Auvray et al the response rates are reported for the overall population so includes patients treated with other VEGFR-TKIs not just with sunitinib (based on 30 assessments).
[c] Classified using the International Metastatic renal cell carcinomas Database Consortium
[d] Reported as the objective response rate, defined as partial responses plus complete responses
Abbreviations: PR: partial response; SD: stable disease; PD: progressive disease.

Table 4 | Survival outcomes from non-comparative studies[10, 12, 15]

Study name	Follow-up, months (95%CI)[a]	Median PFS, months (95%CI)	Median OS, months (95%CI)	Survival rate at 12 months, % (95%CI)[b]
Auvray et al (n=17)	22 (19 to NE)	8 (3 to NE)	11 (5 to NE)	Overall population: 54%
Graham et al (n=17)	Not reported	Median TTD: 5.5 (3.2 to 14.8)	Not reported	78% (46 to 92)
Wells et al (n=62)	5.5 (0.03 to 33.7)	Median TTD: 5.4 (3.6 to 14.8)	16.1 (8.5 to 35.2)	Overall population: 57.5% (45.2 to 68.0)

[a] Median follow-up from start of VEGFR-TKI

[b] Overall population includes patients treated with all VEGFR TKIs at second-line.

Abbreviations: PFS: progression free survival; OS: overall survival; CI: confidence interval; NE: not estimated; TTD: time to treatment discontinuation

Patient reported outcomes

No patient reported outcome data were reported across the included studies.

Safety evidence

Grande et al was the only study which reported safety outcomes for the group of patients treated with sunitinib at second-line so will be described in more detail, however, only a small proportion of patients were treated with ipilimumab plus nivolumab at first-line. The proportion of patients reporting a grade 3 adverse event (AE) was 52% (n=11); no grade 4 or 5 AEs were reported apart from one patient with signs of grade 5 pancytopenia. The most frequently reported treatment-emergent adverse events were diarrhoea (52%), dysgeusia (38%), palmar plantar erythrodysesthesia (38%) and hypertension (38%). Serious adverse events (SAEs) were reported for eight patients (38%). A SAE is any untoward medical occurrence that results in death or is considered life-threatening.[18] Four patients had SAEs that were considered related to sunitinib; bilateral thrombosis, oral mucositis, pancytopenia and rectal bleeding. One patient died with the cause of death reported as pancytopenia. Five patients had at least one dose reduction and 12 (57%) patients had at least one treatment interruption while on sunitinib with a total of 19 interruptions.

Auvray et al reported safety for the full population who received any VEGFR-TKI at second-line. The proportion of patients reporting an adverse event of grade 3 or worse severity was 42%. The most frequent type of grade 3 or 4 AEs reported were cardiovascular such as high-blood pressure (15%), cutaneous such as palmar plantar erythrodysesthesia (12%) and gastrointestinal such as diarrhoea (6%). Graham et al did not include any safety outcomes. Wells et al did not report safety outcomes; only reporting toxicity as a reason for discontinuation in approximately one third of patients (n=10/29).

Sunitinib is licensed for use in the first-line setting, supported by COMPARZ, a phase III non-inferiority study. The safety results for this study note 74% of patients experienced treatment-emergent adverse events (occurring in more than 10% of patients) of grade 3 or worse severity.[19] There were eight (1%) drug-related deaths in the sunitinib group. The most common grade 3 or worse adverse events were thrombocytopenia (22%), neutropenia (20%), fatigue (17%) and

hypertension (15%). This study also presents data on key resource use. The cumulative mean number of days in hospital for sunitinib was 0.56 per patient per month over the first 6 months. This hospitalisation data is used as a proxy in the economic analysis for the second-line use of sunitinib.

Quality assessment of clinical evidence

Overall, on applying the ROBINS-I tool all studies were assessed as having a low risk of bias or a moderate risk of bias.[9] Bias due to confounding was assessed to be high in the studies as no appropriate analysis method was used to control for confounding, most likely due to the small sample sizes of the studies. Bias in measurement of response outcomes was assessed to be moderate as, although this was investigator-assessed based on RECIST v1.1, the outcome measure could have been influenced by knowledge of the intervention received due to lack of blinded or independent centrally assessed outcome data.

Clinical effectiveness considerations

There is a lack of comparative data for second-line sunitinib use

The relative efficacy and safety of sunitinib in second-line treatment following ipilimumab plus nivolumab remains unclear due to the absence of comparative studies. It is unlikely that controlled randomised studies will be conducted to examine the relative efficacy and safety of sunitinib compared to best supportive care in the second-line setting. No estimates for PFS and OS with best supportive care have been identified.

There is significant uncertainty interpreting non-comparative evidence from retrospective cohort studies

- As described in the quality assessment section, the risk of confounding in the studies is high and results need to be interpreted cautiously.
- There was incomplete data on intervals for assessment of progression. Longer intervals between imaging in clinical practice may lead to overestimation of PFS compared to prespecified intervals in prospective trials.
- Outcome measures varied across the studies and PFS and TTD may not be equivalent; TTD may be an underestimate compared to PFS if treatment is stopped prior to the date of assessment of progression, but it may overestimate PFS in cases where a patient is having a clinical benefit and continues treatment despite progression by RECIST criteria.
- The 95% confidence intervals were wide, reflecting the uncertainty with small patient numbers in each study and short follow-up periods. The certainty around these results is further reduced by the mixed patient populations of prior antiangiogenic inhibition (either EGFR or VEGF inhibition) and by prior types of ICI.
- The response rate reported by Graham et al. is higher than other reports in the second-line setting. This may be due to unblinded clinician-assessed response rate, or missing data from non-responders and small sample size, which could potentially overestimate the response rate.

- The retrospective cohort studies and INMUNOSUN-SOGUG included non-clear cell histology but did not provide detailed survival data for patients treated with sunitinib. There is uncertainty regarding relative outcomes in non-clear cell histology.

The available data suggests sunitinib may have clinical activity in the second-line setting.

Objective response rates ranged from 22% to 54% in retrospective cohort studies and 19% in the INMUNOSUN-SOGUG trial. The INMUNOSUN-SOGUG trial did not reach its pre-specified endpoint of an ORR of 30%. This endpoint was based on the response rates in the first-line setting for sunitinib. However, a lower response rate is normally expected with each subsequent treatment line. The INMUNOSUN-SOGUG trial included patients who had demonstrated progression from measurable disease. The retrospective cohort studies did not stipulate that patients had to demonstrate progression prior to initiation of sunitinib, although this would be expected in clinical practice. Outside of pseudo-progression, patients would not normally be expected to have an objective response from BSC after progression on ICI.[20] Pseudo-progression is an ICI phenomenon where a cancer initially appears to worsen on scans despite actually improving. This occurs when there is an inflammatory response that is visible on imaging.

Progression free survival or TTD ranged from 5.4 to 8 months in the retrospective cohort studies and the phase II trial. The ongoing impact of previous ICI to these outcomes, and the relative effect of sunitinib compared to BSC on PFS or TTD or OS is unknown.

The range of PFS and ORR from observational studies and from the phase II clinical trial after first-line ICI is similar to other VEGFR-TKIs used in the relapsed setting.

A recent descriptive systematic literature review found that all VEGFR-TKIs have some evidence supporting their use. Due to the weaknesses in the available evidence formal statistical analysis of the data was not possible. The review also found that treatment line-data were too poorly and inconsistently reported to allow comparison of benefit of VEGFR-TKIs for different lines of treatment in the after ICI pathway.[21]

Overall survival data from the studies are immature

The data on overall survival across the studies were immature. For INMUNOSUN-SOGUG 11 out of the 21 patients were censored on the Kaplan-Meier Curve with a median follow up of 15 months (IQR 7.6 to 24.1); for the study by Auvray et al., 17 out of 33 patients were alive for the whole population with a median follow up of 22 months (95% CI 19 to NE); for the study by Graham et al., 14 out of 17 patients were alive (follow up not reported); and for the study by Wells et al., 37 out of 62 patients were alive with a median follow up of 5.5 months (95%CI 0.03 to 33.7).[10, 12, 15] Most patients across these studies also received subsequent therapies, creating significant uncertainty about whether second-line sunitinib provides an overall survival benefit. For example, in the Grande et al study, nearly 60% of patients received subsequent treatment with cabozantinib.

There is robust evidence of sunitinib efficacy and safety in the first-line setting

The clinical rationale for using sunitinib is supported by robust phase III trial data demonstrating its efficacy and safety in the first-line setting. COMPARZ, a phase III non-inferiority study of 1,110

patients compared pazopanib to sunitinib as first-line therapy and found that pazopanib was non-inferior to sunitinib. The study also showed a progression-free survival (PFS) of 8.4 months with pazopanib (95% CI, 8.3 to 10.9) and 9.5 months with sunitinib (95% CI, 8.3 to 11.1). Partial responses were observed in 170 patients in the pazopanib group (31%) and in 134 in the sunitinib group (24%).[19] Complete responses were observed for 3 patients in the sunitinib group. The PFS and ORR for sunitinib use as a second-line treatment, based on the available data from the retrospective cohort studies and the Phase II trial, is shorter than that observed in first-line treatment. However, a shorter PFS is expected with each subsequent line of therapy.[22] To get a broader sense of the sunitinib safety profile it may be helpful to consider the adverse events reported in the previously untreated, first line population: grade 3 or worse AEs for sunitinib in the COMPARZ trial included thrombocytopenia (22%), neutropenia (20%), fatigue (17%), and hypertension (15%). It is important to note that patients in later lines may be frailer and may experience more AEs with sunitinib than reported in first line use. [19]

The sunitinib safety profile in the proposed population is uncertain but there were no unexpected toxicities

Robust safety reporting in the second-line setting comes from the phase II trial, however, this is based on a study population of only 21 patients.[13] Due to the lack of planned, prospective data collection, the observational studies are less robust for assessing safety. Across the available evidence, the safety profile is similar to the expected toxicities for sunitinib.[10, 12, 15] However, there is significant uncertainty regarding the rates of uncommon and rarer side effects. More generally, the descriptive systemic literature review did not find any new safety signals for VEGFR-TKIs after ICI.[21] Patients may be more likely to experience an adverse event in later lines of treatment due to the residual effects of ICI, increased frailty, and disease burden.

Overall the retrospective cohort studies and the Phase II trial may be generalisable to the Scottish population

Retrospective cohort studies may be more generalisable to the Scottish population due to the unselected nature of patients. Wells et al. and Graham et al. included wider selection criteria, including patients with brain metastases and fewer restrictions for cardiac history.[12, 15]

The proposal is for patients who have progressed on ipilimumab plus nivolumab, which is restricted to use in patients with intermediate or poor-risk renal cell carcinoma. The retrospective cohort studies by Auvray et al., and Graham et al., had greater than 10% of patients with a favourable IMDC risk score.[10, 12] The inclusion of patients with favourable risk may overestimate the effectiveness in the population being considered for treatment in Scotland.

The NHS Scotland Cancer Medicines Outcomes Programme – Public Health Scotland (CMOP - PHS) provided a report of real-world data on Scottish patients with advanced or metastatic renal cell carcinoma treated with sunitinib or pazopanib as a second line treatment following prior first-line treatment with ipilimumab plus nivolumab. Access to treatment with sunitinib was likely through individual patient requests. The patient group data aligned with the published evidence; similarities across baseline characteristics and outcomes may provide reassurance that the

evidence reported from the retrospective cohort studies and INMMUNOSUN-SUGUG are generalisable to Scotland.

4. Patient group summary

Patient group partner (PGP) statements were received from Action Kidney Cancer and Kidney cancer UK, the key points are summarised below:

- Metastatic renal cell carcinoma is a devastating disease and is currently incurable. Symptoms reported include fatigue, depression, weight loss, anorexia, anaemia and pain which varies in severity according to the stage of their disease.
- The spread of cancer can cause severe and debilitating symptoms. Kidney function is often compromised, and patients find daily living difficult. Most patients are forced to give up work and may be faced with financial and psychological challenges.
- There is a lack of routinely accessible treatments for patients in this setting. This causes anxiety for patients, delays and inconsistency in accessing treatments. Access to sunitinib would give these patients an accessible treatment that can be taken at home, a chance at controlling their cancer, more time with their loved ones, and improved psychological wellbeing.
- Sunitinib's side effects can be debilitating and affect quality of life of the patient and their family. Clinicians have a lot of experience of the side effects of VEGFR TKIs and they can be effectively managed or mitigated by the patient together with their hospital team. Patients are willing to accept the chance of side effects for this treatment option.

In summary | introduction of sunitinib would provide a routinely accessible treatment option in this setting.

5. Benefit-risk balance

The relative anticancer and safety effects of sunitinib when compared to best supportive care in this context are unknown. The available evidence from retrospective cohort studies and a phase II trial indicate tumour shrinkage with sunitinib. The strength and certainty of this supporting evidence is limited by mixed patient populations and significant limitations in study design. It is unclear if sunitinib is associated with an overall survival benefit in this patient group due to a lack of comparative evidence, immature data, and confounding by subsequent treatments.

There is no comparative evidence on the safety of sunitinib in the second-line setting after ipilimumab plus nivolumab. Across the available evidence, the safety profile is similar to the expected toxicities for sunitinib. However, there is significant uncertainty due to small patient numbers and retrospective reporting.

There is an unmet need for the treatment of mRCC after ipilimumab plus nivolumab with no routinely accessible treatment options.

6. Council Review |Clinical benefit-risk balance evaluation

After consideration of all the available evidence regarding the clinical benefits and harms, the Council were satisfied with the clinical effectiveness case for this on-label use of sunitinib. Under the decision-making framework for value judgements, Council considered the clinical case to be compelling.

7. Economic Evidence Review Summary

Economic Overview

No relevant economic evidence was identified by our literature search for sunitinib.

Type of Economic Evaluation

Based on the lack of published cost-utility analysis, the clinical evidence, and the expected service implications, a de-novo cost-comparison analysis was performed.

Population, intervention, comparator and outcomes

The population used was patients with poor or intermediate risk advanced/metastatic renal cell carcinoma receiving sunitinib second line who have received ipilimumab in combination with nivolumab as first line treatment. The intervention was six months of sunitinib taken orally, with the comparator being best supportive care. Time on treatment was in line with the median time to treatment discontinuation (TTD) presented in Table 4. Real-world evidence from NHS Scotland was also in line with the time on treatment selected in the model. As a cost-comparison analysis was performed, quality-adjusted life-years (QALYS) were not required in the analysis.

Costs

Sunitinib acquisition costs, monitoring costs and adverse event costs were included. Only CT scans were included for monitoring costs and only adverse events resulting in Accident and Emergency (A&E) department attendances or inpatient stays were included. Adverse event rates for sunitinib were taken from the first line COMPARZ study, and the monitoring from the West of Scotland Cancer Network Systemic Anti-Cancer Therapy Protocol. Costs were not discounted. A&E attendance and inpatient stay costs were taken from Scottish health service cost book. CT scan costs were taken from the National Schedule of NHS Costs.

Results

These exclude VAT.

The medicine acquisition cost of sunitinib per patient was £12,283 (BNF list price). When including administration and monitoring this was figure £15,296 (BNF list price). The Council considered results using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence issues.

Cost-effectiveness considerations

Generalisability of the cost comparison

National Framework contract pricing for generic medicines was used to obtain results of greater relevance.

Limitations of the cost comparison

Due to an absence of a published cost-utility analysis, the cost comparison only compares costs. Sunitinib is a cost-increasing intervention. Given the absence of a quality-adjusted life year estimate, an ICER is not available, and the cost-effectiveness remains unknown.

Only a selection of treatment related adverse events, that is those requiring A&E attendance or hospital admission, were included in the cost comparison. This was done based on the available published information for patients treated first line and may not be the same as for patients treated with sunitinib following prior treatment with ipilimumab plus nivolumab. If including all adverse event costs, the results of the cost-comparison would likely increase.

There is uncertainty around subsequent treatments which may become routinely accessible following second-line treatment with sunitinib. The cost comparison analysis could not include the potential costs of these.

Summary

The cost-comparison indicated that sunitinib is a cost increasing intervention. However, in the absence of an analysis to quantify treatment benefits in relation to costs, an ICER was not available, and the cost-effectiveness remains unknown.

A detailed budget impact analysis, exploring the financial impact of medicine cost in the anticipated population is presented in Section 10.

8. Council review | Cost-effectiveness evaluation

After consideration of the available evidence, the Council accepted that the proposed intervention was cost-increasing relative to best supportive care, and that, in the absence of a cost-effectiveness analysis, the cost-effectiveness remained unknown.

9. Service Impact

The use of sunitinib for this patient population is not expected to have significant service implications. The estimated eligible patient population across NHSScotland is 30 per year. Oral VEGFR-TKIs are already being used for some of this patient population via individual patient requests, and no specific increase in monitoring or dispensing requirements are expected for the use of sunitinib. The service impact of the proposed use is unlikely to be significant.

10.Budget Impact

In the absence of a cost-effectiveness analysis, a detailed budget impact analysis was conducted.

Patient uptake

The number of patients expected to be treated with VEGFR-TKIs was estimated to be 30 in Year 1. This was based on prescribing data from a regional cancer network and extrapolated based on population proportion to give a national figure, and clinician opinion of the eligibility for second line treatments. This number is expected to be consistent on a yearly basis.

Per patient medicine cost and treatment duration

These prices include VAT.

Sunitinib was costed at 50mg daily per cycle of 4 weeks on and 2 weeks off using 28 x 25mg, 1 pack, £1,695 (list prices from BNF, November 2023). These costs were applied for 6 months.

Comparator displacement

As there is no routinely accessible standard of care for this treatment line, and medicines accessed through individual request are not uniform throughout Scotland, no comparator was considered.

Results

In Year 1 the net national medicines budget impact was estimated to be £442k (BNF list price) based on an uptake of 30 patients. In subsequent years the net total budget impact was estimated to be £442k (BNF list price) based on a continuing uptake of 30 patients.

Table 5 | Budget impact analysis base case results

	List price	
	Year 1	Subsequent years
Sunitinib acquisition cost		
Acquisition cost	£14,740[a]	£14,740[a]
Number of patients treated	30	30
Budget Impact		
BUDGET IMPACT - NET MEDICINE COSTS	£442,201	£442,201

[a]based on oral administration of 50mg daily per cycle.

Scenario considerations

The following table presents budget impact scenarios, exploring changes in treatment duration, and annual patient numbers.

Table 6 | Scenario analyses (list prices)

#	Base case	Scenario	Sunitinib acquisition cost per patient	Number of patients treated (Year 1)	Budget impact – Net medicine costs Year 1	Number of patients treated (Steady state)	Budget impact – Net medicine costs steady state
	Base case	-	£14,740	30	£442,201	30	£442,201
1	6 months of sunitinib	4 months of sunitinib	£9,827	30	£294,801	30	£294,801
2	30 patients treated per year in steady state	15 patients treated per year in steady state	£14,740	15	£221,100	15	£221,100
3	6 months of sunitinib and 30 patients in steady state	4 months of sunitinib and 15 patients in steady state	£9,827	15	£147,400	15	£147,400

Limitations

Per patient treatment costs for sunitinib assumed 6 months of treatment, though this varied in literature. A shorter time on treatment was explored and results are shown in budget impact scenario 1.

Patient numbers were estimated and were subject to uncertainty. The base case budget impact results were based on an annual uptake of 30 in Year 1 and 30 in a steady state. This may overestimate the budget impact in the steady state and decreased patient uptake was explored in budget impact scenario 2.

The proposal form noted treatments being accessed through individual requests. Therefore, the Year 1 budget impact of the proposal, which assumes no treatments being displaced, may be overestimated, as some patients may already be receiving treatments and these costs have not been accounted for.

Summary

The use of sunitinib will increase the net medicines budget impact for this patient group when compared to best supportive care. For 6 months of sunitinib use, the medicine acquisition cost was expected to be £442k (BNF list price) per 30 patients.

The Council considered the net medicines budget impact using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the budget impact using confidential pricing due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS pricing.
Separate information will be supplied by the boards to facilitate local budget impact assessment.

11. Council review | Overall proposal evaluation

After consideration of all relevant information under the decision-making framework for value judgements the Council made a decision to support this use.

12.Acknowledgements

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This advice represents the view of the NCMAG Council and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Minor document amendments

Date	Previous version	Amendment	Updated version	Approved by