National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG112 Pazopanib | Advice Document v1.0 | January 2024

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 off-label use of pazopanib is **not supported**

[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 supporting the proposal, the Council considered the justification of the treatment costs in relation to its health and wider benefits were not sufficient to gain support.

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	NHS Scotland Renal Cancer clinicians
Medicine Name	Pazopanib
Cancer type	Renal cell carcinoma
Proposed off-label[B] use	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: Film Coated tablets Dose: 800 mg once daily. Continuous treatment until disease progression or unacceptable toxicity[1]

[B] Pazopanib has marketing authorisation for the following indication:

- First-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.

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. RCCs 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 is the eight 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 (OS) 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 due 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 available for intermediate and poor risk patients in the first-line setting[5].

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 off-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 pazopanib. For non-clear cell RCC, where supporting evidence is less robust, due to smaller patient cohorts, VEGFR-TKIs are also considered acceptable options[2, 6, 7].

In the UK, pazopanib is off-label for second-line use, as its use is restricted to first-line treatment or following cytokine therapy only[1]. It has a broader licence that includes second-line use in the USA, New Zealand and Australia[8-10]. 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 ICI. Therefore, an unmet need exists in the second-line setting for patients previously treated with ipilimumab plus nivolumab with no routinely available treatment options outside of 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 pazopanib

Pazopanib 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 pazopanib, '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 risk of bias in non-randomised studies of interventions (ROBINS-I) tool[11].

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

Overview of evidence for use of pazopanib at second line

Four studies were identified as relevant to this proposal, all of which were retrospective cohort studies. In all but one of the studies the type of first line ICI varied within and between the studies[12-15]. The proportion of patients who received ipilimumab plus nivolumab at first line ranged from 14% to 100% (Table 1). All four studies included patients who received pazopanib second line, ranging from 18% to 70%. The median age of patients included in the studies ranged between 57 years to 63 years, the majority of patients had clear cell histology and were classified as either having an IMDC risk group of intermediate or poor (see Table 2).

Table 1 | Evidence Matrix[12-15]

	First-line therapy ipilimumab plus nivolumab		Second-line therapy pazopanib	
Study, year Study design	**All patients (n)**	**Proportion of patients (n)**	**All patients (n)**	**Proportion of patients (n)**
Auvray et al 2019, Retrospective cohort	✓(33)	-	-	18% (6)
Barata et al 2018, Retrospective cohort[a]	-	33% (11)	-	27% (8)[b]
Cao et al 2020, Retrospective cohort[a]	-	14% (36)		70% (182)[b]
Shah et al 2019, Retrospective cohort[a]	-	47% (33)	-	27% (19)[b]

[a] results are not reported by type of first line therapy. Other 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%);
[b] results are not presented by first line therapy

Auvray et al[12] reported on mRCC patients treated with second line VEGFR-TKI after progressive disease with first-line ipilimumab plus nivolumab treatment in the setting of the Checkmate 214 clinical trial. Outcomes measured included OS, progression-free survival (PFS), response and safety. Results for response outcomes are reported separately for the pazopanib group and either combined with sunitinib or cabozantinib for survival outcomes.

Barata et al[13] reported on consecutive patients with clear-cell mRCC who progressed on one of seven clinical trials investigating an ICI combination regimen and who received ≥1 line of subsequent VEGFR TKI therapy. The first-line therapy received by patients varied and comprised of atezolizumab plus bevacizumab (64%), ipilimumab plus nivolumab (33%) and axitinib plus avelumab (3%). Outcomes measured included PFS, response and safety. Results for the pazopanib group are not reported by type of first-line therapy.

Cao et al[14] reported on patients with advanced RCC who had received 2nd or 3rd line pazopanib after discontinuation with ICI therapy in the United States. The first line ICI received by patients varied and comprised of nivolumab (68%), ipilimumab plus nivolumab (14%), pembrolizumab (12%) or ipilimumab (3%). Outcomes measured included duration of therapy (DOT), PFS, OS, discontinuation and adverse event occurrence. Results for the pazopanib group are not reported by the type of first line therapy.

Shaha et al[15] reported on patients with mRCC treated with second line VEGFR-TKI after progressive disease with first-line ICI in the setting of clinical trials. The first-line therapy received by patients varied and comprised of nivolumab or atezolizumab (17%), ipilimumab plus nivolumab (47%) with the remaining patients receiving either the combination of nivolumab plus bevacizumab or the combination of atezolizumab plus bevacizumab (36%). Outcomes measured included response, PFS, OS and safety after progressive disease. Results for the pazopanib group are not reported by type of first-line therapy.

Common outcomes measured in all the studies were response rates, PFS and OS; these are presented in Tables 2 and 3. To assist the interpretation of the results please refer to Table 1 which details the proportion of patients who received ipilimumab plus nivolumab at first-line and pazopanib at second-line and highlights the studies that do not report results for pazopanib by type of first-line therapy. None of the included studies note the dosage of pazopanib used.

Table 2| Summary of non-comparative studies and response results[12-15]

Study name (n)	Participants (overall, unless stated otherwise)	Response rates		
		PR, n (%)	SD, n (%)	PD, n (%)
Auvray et al France (n=33)	Median age 61 Clear cell 90% Prognostic group • Favourable 15% • Intermediate 64% • Unfavourable 21%	12 (36%)	13 (39%)	5 (15%)
Barata et al USA/UK (n=7)	Median age 57 Clear cell 100% Prognostic group • Favourable 27% • Intermediate 52% • Poor 21%	3 (43%)	2 (29%)	2 (29%)
Cao et al USA (n=182)	Median age 63 Clear cell 100% Prognostic group • Favourable 12% • Intermediate 19% • Intermediate/Poor 22% • Poor 36% • Unknown 12%	NR	NR	NR
Shah et al USA (n=19)	Median age 59 Clear cell 100% Prognostic group • Favourable 11% • Intermediate 69% • Poor 20%	8 (42%)	8 (42%)	3 (16%)

PR: partial response; SD: stable disease; PD: progressive disease; NR: not reported

Table 3 | Treatment and survival results for non-comparative studies[12-15]

Study name, (n)	Follow-up, months (95%CI)[a]	Median DOT, months (95% CI)	Median PFS, months (95%CI)	Median OS, months (95%CI)
Auvray et al (n=6)	22 (19 to NR)	Not reported	5 (1 to NR)[b] 8 (5 to 16)[c]	13 (6 to NR)[b] 11 (6 to NR)[c]
Barata et al (n=9)	13[a]	Not reported	5.6 (1.2 to 10)	Not reported
Cao et al (n=182)	5.1 (0.7 to 16)[a]	13.4 (11.1 to NR)	16 (12 to NR)	Estimated OS rate at 12m: 91%
Shah et al (n=19)	14.9	Not reported	24.4 (6.1 to NR)	OS probability at 12m: 0.89 (0.75 to 1.0)

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

[b] results reported as a combination of pazopanib and cabozantinib

[c] results reported as a combination of pazopanib and sunitinib

CI: confidence interval; DOT: duration of treatment; PFS: progression free survival; OS: overall survival; NR: not reached

Patient reported outcomes

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

Safety evidence

Cao et al[14] reported 57 (31%) of patients discontinued treatment, the primary reason for discontinuation was progression or death in 44 (77%) patients. The most frequently reported (>10%) adverse events with second-line pazopanib were diarrhoea (16%) fatigue (13%), decreased appetite (13%), hypertension (12%), and stomatitis (11%). Auvray et al[12] and Barata et al[13] reported safety for the full population who received any TKI group at second-line, Shah et al[15] reported the safety profile of the 12 patients who discontinued second-line therapy. Five out of the 19 patients treated with pazopanib in the Shah study discontinued second-line pazopanib due to increased liver enzymes.

Pazopanib is licensed for use in the first line setting, supported by a phase III non-inferiority study. The safety results note 74% of patients experienced treatment-emergent adverse events (occurring in more than 10% of patients) of grade 3 or worse severity. There were three (1%) drug-related deaths in the pazopanib group. The most common grade 3 or worse adverse events were increased liver enzymes ALT (17%) and AST (12%), hypertension (16%), and fatigue (11%). The cumulative mean number of days in hospital for pazopanib was 0.40 per patient per month over the first 6 months[16]. This hospitalisation data is used as a proxy in the economic analysis for the second-line use of pazopanib.

Quality assessment of clinical evidence

The evidence to support this proposal came from four retrospective cohorts which is inherently poor in quality, mainly due to the lack of comparative data. Overall, on applying the ROBINS-I tool to all studies, they were either assessed as having a low risk of bias or a moderate risk of bias. Bias due to confounding was assessed to be high in two of the studies as no appropriate analysis method was used to control for confounding, most likely due to the small sample sizes of the studies. Due to the lack of blinded outcome assessment the outcome measure could have been influenced by knowledge of the intervention received.

Clinical effectiveness considerations

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

The relative efficacy and safety of pazopanib 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 pazopanib 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 regarding the strength of 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 compared to prespecified intervals in prospective trials may lead to overestimation of progression free survival.
- Outcome methods varied across the studies; DOT may be an underestimation 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 clinical benefit and continues treatment despite progression by RECIST criteria.
- The 95% confidence intervals were wide or not reached, 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 agents (either EGFR or VEGF inhibitors) and by prior types of ICI.
- Only Auvray et al. included non-clear cell histology but did not provide detailed survival data for patients treated with pazopanib. There is uncertainty regarding relative outcomes in non-clear cell histology[12].
- The 95% lower bound CI for PFS reported by Cao et al[14] exceeds those reported in other studies, which may be due to weaknesses in the study design, including unblinded clinician-assessed response rate or missing data from non-responders. Furthermore, 83% of patients only received single agent ICI in the first-line and it is unknown whether this could affect response to VEGFR-TKIs in the 2nd line setting. Together these suggest that the efficacy of pazopanib in the proposed patient population is likely less than that described by Cao et al. [14].

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

Objective response rates ranged from 36% to 43% in retrospective cohort studies. Separately, a phase II trial reported an ORR of 23% (95% CI 12.3 to 38.0). This unpublished international multicentre study evaluated the efficacy, safety, and quality of life of daily oral pazopanib in patients with advanced and/or metastatic renal cell carcinoma following ICI. The primary endpoint was PFS. The study is closed to recruitment but only recruited 62 patients out of a target of 100 patients. Sixty eight per cent of patients had intermediate or poor risk disease and 25% had prior anti-VEGF therapy[17]. Although the results were presented at the ESMO conference and published on a trials register, they have not yet been presented in a peer-reviewed journal.

The range of median PFS in the retrospective cohort studies and the unpublished Phase II study is wide (5 to 24 months) The phase II study reported a median PFS of 7.5 months (95% CI 3.7 to 12.6)[18]. The wide range in reported PFS indicates significant uncertainty regarding the strength of the estimates. The relative effect of PFS or TTD compared to BSC is unknown.

The range of PFS and ORR from observational studies 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 after ICI[19]. 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.

Overall survival data from the studies are immature

The data on OS across the studies were immature. In the study by Auvray et al 17 out of 33 patients were still alive for the whole population, with a median follow up of 22 months (95% CI 19 to NE))[12]. The median OS for Shah's study was not reached with a median follow up of 14.9 months (95% CI not reported)[15], and Cao et al. reported that the survival data was not robust due to a high rate of censoring with a median follow up of 5.1 months (95%CI 0.7 to 16)[14]. Barata et al. did not report any survival statistics. Furthermore, subsequent therapies were either inconsistently reported or not reported at all[13].

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

The clinical rationale for using pazopanib is supported by robust phase III trial data demonstrating its efficacy and safety in the first-line setting[16]. 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[16]. 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%). Complete responses were observed for 1 patient in the pazopanib group. The PFS and ORR for pazopanib as a second-line treatment, in some of the retrospective cohort studies, is longer than that observed in first-line treatment. This may be due to weaknesses in the study designs and assessment of response or ongoing contribution of ICI effect, as a shorter PFS would normally be expected.

The pazopanib safety profile in the proposed population is uncertain but there may be higher rates of liver toxicity compared to first line use

In the unpublished prospective Phase II trial, 31% of patients reported adverse events that led to treatment withdrawal. Of these, 16% were due to liver abnormalities with Grade 3 or worse liver abnormalities occurring in 24% of patients. Observational studies are less robust for assessing safety due to the absence of planned, prospective data collection. However, five of the 19 patients reported by Shah et al. discontinued due to elevated liver enzymes[15]. This suggests that there may be an increased risk of liver toxicity with pazopanib, possibly due to residual effects from first-line ICI. Due to the small number of patients and the retrospective nature of the observational data, there is significant uncertainty regarding the rates of uncommon and rarer side effects.

Retrospective cohort studies had less restricted patient populations

Retrospective cohort studies may be more generalisable to the Scottish population due to the unselected nature of patients, however Auvray et al., Barata et al and Shah et al only included patients who had been prior enrolled in a clinical trial. Cao et al included non-trial patients only and included patients with brain metastases and cardiovascular disease[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. All the retrospective cohort studies included greater than 10% of patients with a favourable IMDC risk

score, which may overestimate the effectiveness in the population proposed for this 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 pazopanib 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 are generalisable to Scotland.

4. Patient group summary

Patient group partner 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 pazopanib 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.
- Pazopanib'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 pazopanib 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 pazopanib would provide a routinely accessible treatment option in this setting where there is an unmet need.

5. Benefit-risk balance

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

There is no comparative evidence on the safety of pazopanib in the second-line setting after ipilimumab plus nivolumab. Across the available evidence, there is a signal that liver toxicity may be higher than would be expected with the on-label indication. 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 risks, the Council were satisfied that pazopanib is likely to have clinical activity in the second-line setting after first line ICI treatment. 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 pazopanib.

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 pazopanib second line who have received ipilimumab in combination with nivolumab as first line treatment. The intervention was six months of pazopanib taken orally, with the comparator being best supportive care. Time on treatment was in line with the median progression-free survival (PFS) presented in Table 3. 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

Pazopanib 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 pazopanib 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 pazopanib per patient was £13,648 (BNF list price). When including administration and monitoring this was figure was £15,886 (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

NHSScotland PAS prices were 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. Pazopanib 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 pazopanib 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 subsequent.

Summary

The cost-comparison indicated that pazopanib 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 pazopanib 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 this patient population via individual patient requests, and no specific increased monitoring or dispensing requirements are expected for the use of pazopanib. 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-TKI 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.

Pazopanib was costed at 800mg daily using 30 x 400mg, 1 pack, £1,345.2 (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 £491k (BNF list price) based on an uptake of 30 patients. In subsequent years the net total budget impact was estimated to be £491k (BNF list price) based on a continuing uptake of 30 patients.

Table 4 | Budget impact analysis base case results

	List prices	
	Year 1	Subsequent years
Pazopanib acquisition cost		
Acquisition cost	£16,378[a]	£16,378[a]
Number of patients treated	30	30
Budget Impact		
BUDGET IMPACT - NET MEDICINE COSTS	£491,334	£491,334

[a]based on oral administration of 800mg daily.

Scenario considerations

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

Table 5. Scenario analyses (list prices)

#	Base case	Scenario	Pazopanib 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	-	£16,378	30	£491,334	30	£491,334
1	6 months of pazopanib	4 months of pazopanib	£10,919	30	£327,556	30	£327,556
2	30 patients treated per year in steady state	15 patients treated per year in steady state	£16,378	15	£245,667	15	£245,667
3	6 months of pazopanib and 30 patients in steady state	4 months of pazopanib and 15 patients in steady state	£10,919	15	£163,778	15	£163,778

Limitations

Per patient treatment costs for pazopanib 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 pazopanib will increase the net medicines budget impact for this patient group. For 6 months of pazopanib use, the medicine acquisition cost was expected to be £491k (BNF list price) per 30 patients.

The Council considered the net medicines budget impact using confidential pricing 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 considered the justification of the treatment costs in relation to its health and wider benefits were not sufficient to gain support.

12.Acknowledgements

NCMAG would like to acknowledge the patient group partners Action Kidney Cancer and Kidney Cancer UK, for their valuable contribution.

We would also like to acknowledge the data provided by the Cancer Medicines Outcomes Programme – Public Health Scotland, which provided an evidence source and very helpful context for this review.

13.References

1. European Medicines Agency (EMA): Summary of product characteristics: pazopanib: https://www.medicines.org.uk/emc/product/572/smpc.

2. Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. (1569-8041 (Electronic)).

3. Public Health Scotland: Cancer Incidence in Scotland https://www.publichealthscotland.scot/media/12645/2022-04-12-cancer-incidence-report.pdf.

4. Cancer Research UK: Kidney cancer incidence by age https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer/incidence#heading-One.

5. Scottish Medicines Consortium: SMC2153 nivolumab (Opdivo) date approved 10 June 2019 https://www.scottishmedicines.org.uk/medicines-advice/nivolumab-opdivo-fullsubmission-smc2153/.

6. Ljungberg B, Albiges L, Abu-Ghanem Y, Bedke J, Capitanio U, Dabestani S, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2022 Update. Eur Urol. 2022;82(4):399-410. https://doi.org/10.1016/j.eururo.2022.03.006

7. Motzer RJ, Jonasch E, Agarwal N, Alva A, Baine M, Beckermann K, et al. Kidney Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J. 2022;20(1):71-90. 10.6004/jnccn.2022.0001

8. Food and Drugs Administration prescribing information pazopanib Votrient https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022465s-010S-012lbl.pdf.

9. New Zealand data sheet pazopanib votrient https://www.medsafe.govt.nz/profs/Datasheet/v/votrienttab.pdf.

10. Australian Government department of health and aged care Therapeutic goods administration pazopanib Votrient https://www.tga.gov.au/resources/artg/161281.

11. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. 10.1136/bmj.i4919

12. Auvray M, Auclin E, Barthelemy P, Bono P, Kellokumpu-Lehtinen P, Gross-Goupil M, et al. Second-line targeted therapies after nivolumab-ipilimumab failure in metastatic renal cell carcinoma. Eur J Cancer. 2019;108:33-40. https://dx.doi.org/10.1016/j.ejca.2018.11.031

13. Barata PC, De Liano AG, Mendiratta P, Crolley V, Szabados B, Morrison L, et al. The efficacy of VEGFR TKI therapy after progression on immune combination therapy in metastatic renal cell carcinoma. Br J Cancer. 2018;119(2):160-3.

14. Cao X, Tang D, Ratto B, Poole A, Ravichandran S, Jin L, et al. Real-world clinical outcomes of pazopanib immediately after discontinuation of immunotherapy for advanced renal cell carcinoma. Clinical Genitourinary Cancer. 2020;18(1):e37-e45.

15. Shah AY, Kotecha RR, Lemke EA, Chandramohan A, Chaim JL, Msaouel P, et al. Outcomes of patients with metastatic clear-cell renal cell carcinoma treated with second-line VEGFR-TKI after first-line immune checkpoint inhibitors. Eur J Cancer. 2019;114:67-75. https://dx.doi.org/10.1016/j.ejca.2019.04.003

16. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma. New England Journal of Medicine. 2013;369(8):722-31. 10.1056/NEJMoa1303989

17. Powles TB, Oudard S, Grünwald V, Calvo E, Michaelson MD, Burotto M, et al. 718P A phase II study of patients with advanced or metastatic renal cell carcinoma (mRCC) receiving pazopanib after previous checkpoint inhibitor treatment. Ann Oncol. 2020;31:S564. 10.1016/j.annonc.2020.08.790

18. EU Trials register: A prospective international multicenter Phase II study to evaluate the efficacy, safety and quality of life of oral daily pazopanib in patients with advanced and/or

metastatic renal cell carcinoma after previous therapy with checkpoint inhibitor treatment https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-000708-10/results.

19. Albiges L, McGregor BA, Heng DYC, Procopio G, de Velasco G, Taguieva-Pioger N, et al. Vascular endothelial growth factor-targeted therapy in patients with renal cell carcinoma pretreated with immune checkpoint inhibitors: A systematic literature review. Cancer Treat Rev. 2024;122:102652. https://doi.org/10.1016/j.ctrv.2023.102652

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