selpercatinib hard capsules (Retsevmo®)

Eli Lilly and Company Limited

06 October 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

selpercatinib (Retsevmo®) is accepted for restricted use within NHSScotland on an interim basis subject to ongoing evaluation and future reassessment.

Indication Under Review: monotherapy for the treatment of adults with advanced rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.

SMC restriction: for use in treatment-naïve patients who have not previously received a RET-inhibitor or any other systemic treatments for their advanced stage of disease.

In a phase I/II study, in treatment-naive patients with RET fusion-positive NSCLC, selpercatinib was associated with an objective response rate (ORR) of 84%. Final study results and comparative study results are awaited.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

SMC has previously issued not recommended advice (SMC2371) for selpercatinib for use as monotherapy for the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy. This advice remains valid.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Selpercatinib is an inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase. Certain point mutations in RET or chromosomal rearrangements involving in-frame fusions of RET with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers by promoting cell proliferation of tumour cell lines. Selpercatinib inhibited wild type RET and multiple mutated RET isoforms as well as vascular endothelial growth factor receptor (VEGFR)-1 and VEGFR-3.

Selpercatinib received initial conditional marketing authorisation for adults with advanced RET fusion-positive NSCLC who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy. However, this is not recommended for use by SMC (SMC2371). The current submission represents an extension to this licensed indication to include first-line treatment. Selpercatinib is administered orally at a dose based on body weight: 120mg twice daily for patients <50kg and 160mg twice daily for patients ≥50kg. Treatment should be continued until disease progression or unacceptable toxicity. The presence of a RET gene fusion should be confirmed by a validated test prior to initiation of treatment with selpercatinib.[1]

1.2. Disease background

Lung cancer is the third most common cancer in the UK and approximately 80% to 90% of all lung cancers are NSCLC. There are three main subtypes of NSCLC: adenocarcinoma (including non-squamous), squamous cell and large cell carcinoma. Most cases of NSCLC are diagnosed at an advanced or metastatic stage, and prognosis is poor. RET fusions are rare and are estimated to occur in approximately 1% to 2% of all patients with NSCLC. Compared with the general NSCLC population, patients with RET fusion-positive NSCLC tend to be younger and never have smoked. RET rearrangement rarely coincides with other driver alterations. There have been no significant differences reported in progression-free survival (PFS) and overall survival in untreated patients with NSCLC with or without RET fusion positive disease.[2, 3]

1.3. Company proposed position

The submitting company has requested that selpercatinib is restricted for use in treatment-naïve patients with advanced RET fusion-positive NSCLC which encompasses patients who have not previously received a RET inhibitor or any other systemic treatments for their advanced stage of disease.

1.4. Treatment pathway and relevant comparators

Until recently, patients with RET fusion-positive NSCLC have received the same standard of care therapy as patients with NSCLC without other targetable oncogenic driver mutations. First-line, therapy options that have been accepted for use or restricted use by SMC include:

- pembrolizumab monotherapy (if PD-L1 ≥50% and no epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK] positive tumour mutations; SMC1239)
- pembrolizumab in combination with platinum-based chemotherapy and pemetrexed (if PD-L1 <50%; SMC2207)

- platinum-based chemotherapy and pemetrexed without immunotherapy (if immunotherapy is contra-indicated or there is no PD-L1 expression; SMC531)
- atezolizumab (if PD-L1 ≥50% or ≥10% tumour-infiltrating immune cells and do not have EGFR mutant or ALK-positive NSCLC; SMC2379).

More recently pralsetinib (another RET inhibitor) was licensed for use as monotherapy for the treatment of adult patients with RET fusion-positive advanced NSCLC not previously treated with a RET inhibitor and this was accepted for use on an interim basis within NHSScotland by SMC in March 2023 (SMC2496).[4]

1.5. Category for decision-making process

Eligibility for interim acceptance decision option.
Selpercatinib has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA).

Eligibility for a PACE meeting
Selpercatinib meets SMC end of life criteria and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of selpercatinib for the treatment of RET fusion-positive NSCLC in treatment-naïve patients comes from a cohort of LIBRETTO-001.[2, 5] Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies[1, 2, 5]

Criteria	Cohort of LIBRETTO-001
Study Design	An open-label, single-arm phase I/II multi-cohort study
Eligible Patients	Patients aged ≥18 years with RET fusion-positive NSCLC, who had received no prior therapy. They had measurable disease assessed by investigator according to RECIST v1.1 and ECOG performance status ≤2. Patients with stable CNS metastases were eligible.
Treatments	In phase I (dose-escalation), patients received selpercatinib 20mg once daily to 240mg twice daily. In phase II, all patients (n=69) received selpercatinib 160mg twice daily.
Randomisation	Not applicable.
Primary outcome	ORR defined as the proportion of patients with a best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) based on RECIST v1.1 assessed by independent review committee.
Secondary outcomes	• Duration of response • Progression-free survival • Overall survival
Statistical analysis	ORR was compared with results from historical control. Secondary outcomes are descriptive only.

RET= rearranged during transfection; NSCLC=non-small cell lung cancer; RECIST=response evaluation criteria in solid tumors; ECOG=Eastern Co-operative Oncology Group; CNS=central nervous system; ORR=objective response rate.

Available evidence from interim analysis at the latest data cut-off (June 2021), when patients had been followed for ≥6 months after the first selpercatinib dose, found an objective response rate

(ORR) of 84% in treatment-naïve patients with RET fusion-positive NSCLC. [1, 2, 5] Details of results for primary and secondary outcomes are summarised in Table 2.2.

Table 2.2. Results for the primary and secondary outcomes as assessed by IRC in treatment-naïve RET fusion-positive patients in LIBRETTO-001 at data cut-off June 2021[1, 2, 5]

	Treatment-naïve patients (n=69)
Primary outcome: ORR	
Median duration of follow-up, months	20.3
ORR, % (n/N) (95% CI)	84% (58/69) (73% to 92%)
Complete response, % (n/N)	5.8% (4/69)
Partial response, % (n/N)	78% (54/69)
Secondary outcomes	
Median duration of response (95% CI), months	20.2 (13.0 to NE)
PFS	
Median duration of follow-up, months	21.9
Number of PFS events	32
Median PFS (95% CI), months	22.0 (13.8 to NE)
KM estimated PFS at 12-months	71% (58% to 80%)
KM estimated PFS at 24 months	42% (27% to 56%)
Overall survival	
Median duration of follow-up, months	25.2
Number of deaths	20
Median overall survival (95% CI), months	NE (27.9 to NE)
KM estimated survival at 12-months	93% (83% to 97%)
KM estimated survival at 24 months	69% (55% to 80%)
KM estimated survival at 36 months	57% (36% to 74%)

ORR=objective response rate; IRC=independent review committee; CI=confidence interval; PFS=progression-free survival; KM=Kaplan-Meier.

There were 16 treatment-naïve patients with central nervous system (CNS) metastases determined by the investigator at baseline. In the five patients with measurable CNS disease, the CNS ORR was reported as 80% (95% confidence interval [CI]: 28% to 99.5%) and the CNS duration of response was a median of 9.0 months (95% CI: 5.1 to 15.3). In the 11 patients with non-measurable CNS disease, the CNS ORR was reported as 27% (95% CI: 6.0% to 61%) and the median CNS duration of response was not reached after a median follow-up of 21 months.[2]

2.2. Evidence to support the positioning proposed by the submitting company

The evidence presented in Table 2.2 represents results for the cohort of LIBRETTO-001 of treatment-naïve patients with RET fusion-positive NSCLC and this supports the positioning proposed by the submitting company.

2.3. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) as an exploratory

outcome. Results have not been published but have been presented for health technology appraisal.

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing selpercatinib with (a) pemetrexed plus platinum chemotherapy; and (b) pembrolizumab combination chemotherapy, the submitting company presented indirect treatment comparisons. This created a pseudo arm (pemetrexed plus platinum chemotherapy) for LIBRETTO-001 which was then used to connect selpercatinib to a network meta-analysis (NMA). These results have been used to inform the economic base case.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Propensity score matching was used to create a pemetrexed plus platinum chemotherapy pseudo arm for LIBRETTO-001 which was then used to connect selpercatinib to an NMA.
Population	Treatment-naïve, adult patients with locally advanced or metastatic non-squamous NSCLC.
Comparators	Pemetrexed plus platinum based chemotherapy and pembrolizumab plus pemetrexed plus platinum based chemotherapy
Studies included	31
Outcomes	ORR, PFS and overall survival.
Results	Results suggest that selpercatinib was associated with greater odds of a response and lower risk of progression or death compared with comparators. *_results of the NMA were considered confidential by the company_.

NMA=network meta-analysis; NSCLC=non-small cell lung cancer; ORR=objective response rate; PFS=progression-free survival.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

Safety was assessed in the overall safety analysis set (n=796), which included all patients who were enrolled in LIBRETTO-001 (regardless of tumour type or treatment history) and received one or more doses of selpercatinib at June 2021 cut-off date. There were 356 patients in the safety population who had RET fusion-positive NSCLC and 69 of these patients were treatment-naïve. The median duration of treatment was 21.3 months (19.1 months in RET-fusion positive NSCLC patients [n=356] and 18.5 months for treatment-naïve RET fusion-positive NSCLC patients [n=69]). Any treatment-emergent adverse event (AE) was reported by 99.9% (795/796) of all patients; 100% (356/356) of RET-fusion positive NSCLC patients; and 100% (69/69) of treatment-naive patients and these were considered treatment-related in 95%, 96% and 97% respectively. Patients reporting a grade 3 or higher AE were 72% in all patients, 74% in RET-fusion positive NSCLC patients and 72% of treatment naïve patients, patients with a reported serious AE were 44%, 49% and 38% of patients respectively and patients permanently discontinuing therapy due to an AE were 8.0%, 9.6% and 10%, respectively.[2]

At the 15 June 2021 cut-off date, the most frequently reported treatment-emergent AEs of any grade in the overall safety analysis set (n=796) and the RET fusion-positive NSCLC patients (n=356) were: oedema (48% and 50%), diarrhoea (47% and 52%), fatigue (46% and 43%), dry mouth (43% and 46%), hypertension (41% and 40%), aspartate transaminase (AST) increased (37% and 42%),

alanine transaminase (ALT) increased (36% and 41%), constipation (33% and 27%), rash (33% and 37%), nausea (31% and 31%), blood creatinine increased (29% and 26%), headache (28% and 26%), cough (23% and 24%), dyspnoea (22% and 24%), vomiting (22% and 22%) and electrocardiogram (ECG) QT prolonged (21% and 21%).[2, 5, 6]

Details of treatment-emergent AEs were not reported separately for the 69 treatment-naïve RET fusion-positive NSCLC patients but the overall safety profile in these patients was reported to be consistent with the overall safety population.[2]

In the total safety population, only one of the 45 AEs with a fatal outcome was considered treatment-related: a patient with RET-mutant medullary thyroid cancer who died because of acute respiratory failure.[2, 5]

In view of the AEs seen in LIBRETTO-001, the summary of product characteristics (SPC) recommends monitoring of liver enzymes, blood pressure and the QT interval.[1]

Grade ≥3 haemorrhagic events were reported in 3.1% of patients receiving selpercatinib, including four (0.5%) patients with fatal haemorrhagic events (two cerebral haemorrhage, one tracheostomy site haemorrhage, and one haemoptysis). The SPC recommends that selpercatinib is discontinued in patients with severe or life-threatening haemorrhage.[1]

*Other data were also assessed but remain confidential.**

4. Summary of Clinical Effectiveness Considerations

The key strengths and uncertainties of the clinical case are summarised below:

4.1. Key strengths

- The primary outcome of LIBRETTO-001, ORR assessed by IRC, was achieved by 84% (58/69) of treatment-naïve patients with RET fusion-positive NSCLC which was considered to be clinically meaningful. In a small number of patients with CNS metastases, clinically meaningful CNS responses were also seen which were considered to offer a significant advantage over chemotherapy.[2, 5]
- Selpercatinib is one of two RET inhibitor medicines licensed specifically for RET fusion-positive NSCLC.

4.2. Key uncertainties

- Evidence for treatment-naïve RET fusion-positive NSCLC comes from a small number of patients (n=69) in a supplementary analysis set of the phase I/II, single-arm, open-label study, LIBRETTO-001, which is prone to various biases. Interpretation of all outcomes was hampered by the lack of a control group. Assessment of safety and subjective outcomes, such as quality of life, was limited by the open-label design.[2, 5]
- Depending on bodyweight (<50kg or ≥50kg), the recommended dose of selpercatinib is 120mg or 160mg twice daily. However, in phase II of LIBRETTO-001, all patients received selpercatinib 160mg twice daily, unless reduced due to toxicity.[1, 5]

- Median duration of follow-up is currently limited to approximately 2 years and the data for clinically relevant secondary outcomes of PFS and overall survival are currently immature with only 32 and 20 patients having reached respective events; remaining patients are censored.[2, 5]
- The available data are uncontrolled resulting in uncertainties in the relative safety of selpercatinib. However, the overall safety profile of selpercatinib in treatment-naïve patients was found to be consistent with the overall safety population of LIBRETTO-001. The SPC recommends monitoring of AST and ALT levels, serum electrolytes, blood pressure and ECG.[1, 2]
- There are no direct comparative data, therefore indirect evidence was used to compare selpercatinib with pemetrexed plus platinum-based chemotherapy and pembrolizumab combination chemotherapy. The company concluded that selpercatinib would provide superior efficacy in terms of prolonged PFS and overall survival over these comparators in treatment-naïve patients with RET fusion-positive advanced NSCLC. However a number of methodological and heterogeneity issues limit the robustness of the results, including the use of immature survival data for selpercatinib. Due to the single-arm design of LIBRETTO-001, the company created a propensity score matched, pemetrexed plus platinum chemotherapy, pseudo arm from KEYNOTE-189. However, due to a lack of data, this did not match for RET fusion status in KEYNOTE-189. The comparison with pembrolizumab plus pemetrexed plus platinum chemotherapy relied on connection to the NMA via this pseudo arm, increasing the uncertainty. The indirect comparison population is broader than the licensed indication including study populations regardless of RET fusion status. The company provided supporting references demonstrating that no evidence exists to confirm that RET fusion-positive patients have better outcomes. The licence for selpercatinib does not specify non-squamous disease but this is not expected to significantly restrict the eligible population since most RET fusions occur in patients with adenocarcinoma, which along with large cell carcinoma, is classified as non-squamous histology. There was heterogeneity in the proportions of female and Asian patients across included studies. There was no comparison of safety or quality of life outcomes. Due to these limitations, the company's conclusions are uncertain.

4.3. GB/EMA conditional marketing authorisation specific obligations

The MHRA specific obligations are to provide final results of the LIBRETTO-001 study by December 2023 and to provide results of a phase III study (LIBRETTO-431) comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab in treatment-naïve patients with locally advanced or metastatic, RET-fusion-positive non-squamous NSCLC by December 2024.[7, 8] This may address the key uncertainties in the clinical evidence presented.

4.4. Clinical expert input

Clinical expert input to SMC suggested that selpercatinib is a therapeutic advancement.

4.5. Service implications

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information**.**

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of selpercatinib, as an orphan-equivalent and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- RET fusion-positive advanced NSCLC is a rare cancer that typically presents in non-smoking, younger patients, who usually have family and work commitments. It is incurable with current standard immunotherapy plus chemotherapy, which doesn't target RET mutations, is associated with limited survival, has substantial adverse effects and requires many hospital visits for administration and monitoring. There is an unmet need for therapies that are more effective, tolerable and convenient.

- Selpercatinib targets RET mutations and is associated with high rates of response, including those in the CNS, when used as first-line therapy for RET fusion-positive advanced NSCLC. The duration of response is typically much greater than standard immunotherapy plus chemotherapy regimens. Tolerability of selpercatinib is improved compared with these regimens and, as it can be taken orally at home, it has a more convenient method of administration.

- Selpercatinib may provide an extended period when the patient is well and their disease controlled, which would be further enhanced by the improved tolerability, convenient administration and fewer hospital visits. As selpercatinib is particularly effective in controlling CNS metastases, which are markedly debilitating, it can have profound benefits for the patient's symptoms and care needs. This may provide the patient with more opportunities to socialise, work and care for dependents. It may provide practical benefits for the patient and their family or carer and help reduce the emotional impact of the disease.

- Many patients and their families are aware of selpercatinib and its novel targeted mechanism of action. Accessing a therapy that specifically targets their cancer's mutation may provide reassurance that optimum therapy is being used. It may provide hope that the prolonged response may bridge to a time when additional novel therapies become available.

- Clinical experts advised that selpercatinib would be used in the proposed positioning as a first-line treatment. They noted that its introduction would reduce the number of patients attending hospital for immunotherapy plus chemotherapy in this setting. They advised that there is established clinical expertise in the use of tyrosine kinase inhibitor medicines, such as selpercatinib, and that side effects and monitoring can be managed. It was noted that services are in development for RET testing in NHS Scotland.

Additional Patient and Carer Involvement

We received patient group submissions from the Roy Castle Lung Cancer Foundation and the Scottish Lung Cancer Nurses Forum. The Roy Castle Lung Cancer Foundation is a registered charity and the Scottish Lung Cancer Nurses Forum is an unincorporated organisation. The Roy Castle Lung Cancer Foundation has received 8% pharmaceutical company funding in the past two years, including from the submitting company. The Scottish Lung Cancer Nurses Forum has not received any pharmaceutical company funding in the past two years. Representatives from both

organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (25 years)
Population	Adults with advanced RET fusion-positive NSCLC who have not been previously treated with a RET inhibitor and are treatment-naïve.
Comparators	Current standard of care in UK at first-line: pemetrexed plus platinum chemotherapy as first comparator; pembrolizumab plus pemetrexed plus platinum chemotherapy as second comparator.
Model description	The economic analysis used a partitioned survival model with three health states (progression free, progressed and death) with a one week cycle length. The model adopted an NHS Scotland and social care perspective.
Clinical data	The primary source of clinical data for selpercatinib in the economic model was the LIBRETTO-001 study, based on results from the June 2021 data cut. Due to the absence of direct evidence versus comparators, a pseudo-matched reference arm was generated to complement the PFS and overall survival data generated for selpercatinib from LIBRETTO-001.
Extrapolation	Parametric survival functions were applied in order to extrapolate PFS and overall survival for selpercatinib and the pemetrexed plus platinum chemotherapy arm. In order to generate extrapolations for pembrolizumab combination therapy, the HR generated through the NMA was applied to the survival estimates of the premetrexed arm. The best fitting curve was selected based on statistical fit, visual fit and clinical expert validation. The Gompertz and one-knot spline overall survival were selected as the base case survival curves across all comparators for PFS and overall survival respectively. An exponential curve was selected as the time to treatment discontinuation (TTD) base case for selpercatinib.
Quality of life	Utility values were based on EORTC QLQ-C30 data from the LIBRETTO-001 study, which were mapped onto the EQ-5D-3L UK value set. Alternative values from an appraisal for osimertinib in untreated EGFR mutation positive NSCLC were tested in scenario analysis.[9]
Costs and resource use	The economic analysis included costs associated with medicine acquisition, administration, health-state monitoring, subsequent treatments, adverse events and terminal care. While the company stated that RET fusion testing is becoming increasingly common in Scottish practice, testing costs were included in the analysis.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price. A PAS discount is in place for pembrolizumab and this was included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

The base case analysis results, including the PAS discount on selpercatinib but excluding that on pembrolizumab, produced an incremental cost-effectiveness ratio (ICER) of £35,883 versus pemetrexed plus platinum chemotherapy and £5,264 versus pembrolizumab combination therapy.

6.3. Sensitivity analyses

In deterministic one-way sensitivity analysis, the parameters with greatest impact on ICER were discount rates, drug administration costs and adverse event costs. A range of scenario analyses were performed and presented in Table 6.2. These results include the PAS discount on selpercatinib only.

Table 6.2 Scenario analyses results (PAS for selpercatinib only)

	Scenario	ICER vs pembrolizumab combination therapy (£/QALY)	ICER vs pemetrexed + platinum chemotherapy (£/QALY)
-	*Base case*	*£5,264*	*£35,883*
1	Discount rate: 1.5%	£7,258	£34,855
2	Alternate utilities (TA654)[9]	£5,539	£37,603
3	Alternate curve choice PFS- Weibull	£7,974	£36,105
4	Alternate curve choice PFS- Exponential	£3,995	£35,587
5	Alternate curve choice OS- Spline Knot 3	£4,923	£39,466
6	Alternate curve choice OS- Exponential	£5,412	£33,563
7	Alternate curve choice TTD- Gompertz	Dominated	£30,068
8	Alternate subsequent therapy distribution	£5,194	£39,542

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year; TTD, time to treatment discontinuation

*Other data were also assessed but remain confidential.**

6.4. Key strengths

The main strengths of the economic analysis were:

- The economic model used an appropriate structure which captured disease progression.
- Appropriate sources were selected to inform the model parameters.
- The model incorporated latest available data from the LIBRETTO-001 study.

6.5. Key uncertainties

The main weaknesses of the economic analysis were:

- The clinical evidence was limited to a small subgroup of 69 patients in a single-arm, open-

label study, which was at high risk of bias. Median duration of follow-up was limited to approximately 2 years and the data for clinically relevant secondary outcomes of PFS and overall survival were immature. It was difficult to draw conclusions regarding the clinical effectiveness of selpercatinib due to the uncontrolled nature of the data. The extrapolated survival estimates informing the model were therefore highly uncertain and lacked internal validity.

- There was no direct comparative evidence available and a number of methodological and heterogeneity issues limit the robustness of the ITC results. The results of the ITC were uncertain because of underlying differences in baseline characteristics and RET fusion mutation status between patients in KEYNOTE-189 and LIBRETTO-001. This in turn affected the validity of the NMA, since had other sources been used to inform the comparison with pemetrexed plus platinum-based chemotherapy, the NMA may have had different results. No sensitivity analysis was performed to test the uncertainty around the hazard ratios.
- There was substantial uncertainty regarding the company's choice of survival curves for modelling treatment effectiveness. Using a visual and statistical fit of the parametric curves alone was insufficient to select the most appropriate curves due to the immaturity of data and the choice was informed by clinical expert opinion and alignment to available real-world data. However, there appeared to be several discrepancies between the survival estimates stated by the experts with those predicted by the base case curves for the two comparators.

7. Conclusion

The Committee considered the benefits of selpercatinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as selpercatinib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted selpercatinib for restricted use in NHSScotland, subject to ongoing evaluation and future reassessment.

8. Guidelines and Protocols

The National Institute for Health and Care Excellence (NICE) published Lung cancer: diagnosis and management (NG 122) in March 2019, which was updated in March 2023.[10] The guidance makes specific recommendations for RET fusion-positive NSCLC, depending on PD-L1 status.

The European Society for Medical Oncology (ESMO) published "oncogene-addicted metastatic non-small cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up" in January 2023.[11]

The Scottish Intercollegiate Guidelines Network (SIGN) published Management of lung cancer: A national clinical guideline (SIGN 137) in 2014.[12] The SIGN guideline predates the availability of immunotherapy.

9. Additional Information

9.1. Product availability date

26 October 2022

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
selpercatinib	**120mg or 160mg orally twice daily**	**85,176 to 113,568**

Costs from BNF online on 22 June 2023. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact 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. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 11 August 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium 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.