Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2371

selpercatinib 40mg and 80mg hard capsules (Retsevmo®)

Eli Lilly and Company Ltd

08 October 2021

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 not recommended for use within NHSScotland.

Indication under review: 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.

In a phase I/II study, in previously treated patients with RET-fusion positive NSCLC, selpercatinib was associated with an objective response rate of 64%.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic case to gain acceptance by SMC.

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

Vice Chairman
Scottish Medicines Consortium

Indication

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.[1]

Dosing Information

The recommended dose of selpercatinib based on body weight is:

- Less than 50kg: 120mg twice daily.
- 50kg or greater: 160mg twice daily.

The capsules should be swallowed whole and can be taken with or without food. 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 for NSCLC.

Selpercatinib therapy should be initiated and supervised by physicians experienced in the use of anti-cancer therapies.

The Summary of Product Characteristics (SPC) includes details of recommended dose modifications to manage adverse reactions.[1]

Product availability date

March 2021

Selpercatinib meets SMC orphan equivalent and end of life criteria for this indication.

Selpercatinib has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency.

Summary of evidence on comparative efficacy

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 inhibits wild type RET and multiple mutated RET isoforms as well as vascular endothelial growth factor receptor (VEGFR)-1 and VEGFR-3.[1, 2]

The submitting company has requested that SMC considers selpercatinib when positioned as monotherapy for the treatment of adults with advanced (stage IIIb/IV), non-squamous, RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following one or more prior treatment with immunotherapy and/or platinum-based chemotherapy.

The evidence supporting the efficacy and safety of selpercatinib in NSCLC comes from LIBRETTO-001, an ongoing, open-label, single-arm, phase I (dose escalation) and phase II (dose expansion) study in patients with RET-altered cancers. Eligible patients were aged ≥12 years with a locally advanced or metastatic solid tumour who had progressed on or were intolerant to standard therapy, or no standard therapy existed, or they were not candidates for or were unlikely to tolerate or derive significant clinical benefit from, or had declined, standard therapy. For patients enrolled in phase II of the study, evidence of RET gene alteration in tumour was required. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 to 2 or a Lansky Performance Score (LPS) ≥40%. The study included a cohort of patients relevant to the indication under review with RET fusion-positive NSCLC that had progressed on or were intolerant to at least one prior standard therapy (platinum-based chemotherapy). During phase II, eligible patients were treated with open-label selpercatinib 160mg orally twice daily, continued until disease progression, death, unacceptable toxic effects, or withdrawal of consent. Patients with documented disease progression could continue selpercatinib if the investigator considered they were deriving clinical benefit.[2, 3]

The primary outcome was objective response rate (ORR, defined as the proportion of patients with best overall response [BOR] of confirmed complete response [CR] or confirmed partial response [PR]), assessed by independent review committee (IRC) using Response Evaluation in Solid Tumours Version 1.1 (RECIST v1.1) between date of the first selpercatinib dose and the date of data cut-off, documented disease progression or subsequent therapy or cancer-related surgery. Analyses were performed according to the intention-to-treat principle in the primary analysis set which comprised the first 105 consecutively treated patients across both phase I and II with RET fusion-positive NSCLC, who had received at least one prior line of prior platinum-based chemotherapy. Additional analyses were performed in the integrated analysis set (n=184 at 16 December 2019 data cut-off; n=218 at 30 March 2020 data cut-off), which comprised all primary analysis set patients and those treated after the 105th patient until the data cut-off.

Results of the primary outcome and relevant secondary outcomes, which included duration of response, progression free survival (PFS) and overall survival, are detailed in Table 1 below for the RET fusion-positive NSCLC primary and integrated analysis sets at data cut-offs at 16 December 2019 and 30 March 2020.

Table 1: Results for the primary outcome (ORR) and secondary outcomes in the primary and integrated analysis sets in NSCLC patients in LIBERTRO-001 at data cut-offs at 16 December 2019 and 30 March 2020[2, 3]

Data cut-off	**16 December 2019**		**30 March 2020**	
Analysis set	**Primary analysis set (n=105)**	**Integrated analysis set (n=184)**	**Primary analysis set (n=105)**	**Integrated analysis set (n=218)**
Primary outcome: ORR by IRC				
Median duration of follow-up, months	12.1	9.2	15.7	12.0
ORR, % (N/n) (95% CI)	64% (67/105) (54% to 73%)	57% (104/184) (49% to 64%)	64% (67/105) (54% to 73%)	57% (124/218) (50% to 64%)
CR, % (N/n)	1.9% (2/105)	-	2.9% (3/105)	4.1% (9/218)
PR, % (N/n)	62% (65/105)	-	61% (64/105)	53% (115/218)
Duration of response by IRC				
Duration of response (IRC), months (95% CI)	(n=67) 17.5 (12.0 to NE)	(n=104) -	(n=67) 17.5 (12.1 to NE)	(n=124) 17.5 (12.1 to NE)
PFS by IRC				
Median duration of follow-up, months	13.9	-	16.8	13.6
Number of PFS events	44	-	50	74
Median PFS (IRC), months (95% CI)	16.5 (13.7 to NE)	-	19.2 (13.9 to NE)	19.3 (16.5 to NE)
≥12 months PFS rate	66%	-	66%	70%
Overall survival				
Median duration of follow-up, months	-	-	19.9	14.3
Number of deaths	-	-	28	41
Median overall survival, months (95% CI)	-	-	NE (25.7 to NE)	NE (25.7 to NE)
≥12 months survival rate	-	-	88%	88%

IRC= independent review committee; PFS=progression-free survival; ORR=objective response rate; CI=confidence interval; CR=complete response; PR=partial response; NE=not estimable

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) for adults as an exploratory outcome, which suggested that more patients reported an improvement compared to a worsening.[2]

The submitting company provided indirect evidence to compare selpercatinib with docetaxel monotherapy and nintedanib plus docetaxel in patients with advanced or metastatic NSCLC eligible for second or a subsequent-line therapy, which they considered the most relevant comparators. An unanchored indirect treatment comparison (ITC) was undertaken to compare selpercatinib with docetaxel. Individual patient level data (IPD) for selpercatinib were drawn from LIBRETTO-001[3] and for docetaxel from the REVEL study (ramucirumab plus docetaxel versus docetaxel regardless of RET status).[4] The submitting company used data from the Flatiron Clinico-Genomic Database (CGDB) to adjust IPD for docetaxel from REVEL, via multivariate analysis, to create a pseudo docetaxel control arm reflecting RET fusion-positive status NSCLC. Propensity score weighting, using multivariable regression, was then used to adjust the docetaxel data for other prognostic factors to match LIBRETTO-001. The reported outcomes of the ITC were PFS and overall survival; it was not possible to suitably adjust ORR data. The results of the ITC were used to indirectly compare selpercatinib with docetaxel and also then to connect selpercatinib via docetaxel to Bayesian network meta-analyses (NMA) performed to compare selpercatinib with nintedanib plus docetaxel for ORR, PFS and overall survival (which included the LUME-Lung 1 study: docetaxel versus nintedanib plus docetaxel). The NMA was performed in patients regardless of RET status. The results of the ITC and NMA suggest that selpercatinib was superior to docetaxel monotherapy and nintedanib plus docetaxel for all three outcomes.

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

Summary of evidence on comparative safety

No comparative safety data are available. According to the European Medicines Agency (EMA), selpercatinib presents substantial toxicity; however, its safety profile was considered consistent with that observed for other tyrosine kinase inhibitors, with significant gastrointestinal toxicities, hypertension, increased transaminases and QT interval prolongation. Overall, the EMA considered that the safety profile of selpercatinib in adult patients was manageable. Uncertainties remain and will be addressed by the specific obligations being imposed in the context of the conditional marketing authorisation.

Safety was assessed in the overall safety analysis set (n=746), 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 as of the 30 March data cut-off date. The median duration of treatment was 11.1 months (10.5 months in RET-fusion positive NSCLC patients [n=345]). Any treatment-emergent adverse event (AE) was reported by 99% (740/746) of all patients (100% [344/345] in RET-fusion positive NSCLC patients) and these were considered treatment-related in

92% (93% in RET-fusion positive NSCLC patients). Patients reporting a grade 3 or higher AE were 60% (61% in RET-fusion positive NSCLC patients), patients with a reported serious AE were 35% (39% in RET-fusion positive NSCLC patients), and patients permanently discontinuing therapy due to an AE was 6.0% (7.2% in RET-fusion positive NSCLC patients).[2]

At the 30 March 2020 cut-off date, the most frequently reported treatment-related AEs of any grade with an incidence >10% in the overall safety analysis set (n=746) were: dry mouth (36%), hypertension (26%), aspartate transaminase (AST) increased (26%), alanine transaminase (ALT) increased (26%), diarrhoea (22%), fatigue (19%), oedema peripheral (14%), electrocardiogram (ECG) QT prolonged (14%), constipation (13%), blood creatinine increased (12%), rash (12%), and nausea (10%).[2]

At the 30 March 2020 data cut-off, 14% (104/746) of patients had died, including 56 patients with RET fusion-positive NSCLC. The main reported reason for death were disease progression (67% [70/104]) and adverse event (24% [25/104]). The EMA noted that although the population was too small to draw any precise conclusions, the number of deaths was higher in NSCLC patients than in the medullary thyroid cancer population of LIBRETTO-001.[2]

Summary of clinical effectiveness issues

Approximately 85% to 90% of lung cancers are NSCLC of which there are three main subtypes: adenocarcinoma, squamous cell and large cell. The majority of lung cancers are diagnosed at an advanced stage and prognosis is poor. RET fusions are rare and are estimated to occur in approximately 1% to 2% of all NSCLC. Patients with RET fusion-positive lung cancer tend to be younger than the general NSCLC population and to have never smoked. In addition RET fusions appear to be mutually exclusive of other oncogenic drivers, including EGFR, ROS1 and KRAS mutations. Patients with RET fusion-positive lung cancer commonly have brain metastases at rates similar to the overall NSCLC population, in approximately 20 to 50% patients. Patients with RET fusion-positive NSCLC currently receive the same standard of care therapy as patients with NSCLC without other oncogenic driver, including first-line therapy with platinum-based chemotherapy or immunotherapy followed by second-line and subsequent treatment with docetaxel, nintedanib, pemetrexed or immunotherapy, depending on what has been used previously.[2] Selpercatinib is the first targeted therapy for previously treated patients with RET fusion-positive disease, clinical experts consulted by SMC considered that selpercatinib fills an unmet need in this therapeutic area as a targeted therapy. They consider selpercatinib a therapeutic advancement due to the targeted mechanism of action and consider its place in therapy for patients who have disease with the relevant mutation. Selpercatinib meets SMC orphan equivalent and end of life criteria.

The submitting company has requested SMC to consider selpercatinib when positioned for patients with advanced (stage IIIb/IV) non-squamous disease. This is not expected to significantly restrict the eligible patient population since most RET fusions occur in patients with adenocarcinoma, which along with large cell carcinoma, is classified as non-squamous histology. This reflects the NSCLC patient population of LIBRETTO-001.

The introduction of selpercatinib may be associated with service implications, due to various monitoring requirements (including AST, ALT levels, blood pressure, ECG and serum electrolytes) although patient numbers are expected to be low. Companion diagnostic testing for RET alterations is required: contact local laboratory for information.

Key strengths

- In the RET fusion-positive NSCLC primary and integrated analysis sets, in patients who had previously received platinum-based chemotherapy, the ORR were 64% and 57%, respectively (data cut-off 16 December 2019). Results were confirmed on updated analyses using the March 2020 data cut-off. The observed effects were relevant in patient population with advanced disease, many of whom had been heavily pre-treated and the EMA considered that major therapeutic advantage was demonstrated.
- Selpercatinib is the first medicine to be approved specifically for RET fusion-positive NSCLC.

Key uncertainties

- Evidence is provided from a small subgroup (n=105) of a 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 subjective outcomes such as quality of life and safety was limited by the open-label design.
- Median duration of follow-up was limited and the data for the supportive secondary outcome of overall survival are currently immature.
- Some factors may affect the generalisability of study results to clinical practice including half of study patients having received three or more lines of previous systemic therapy. In addition, about half of study patients were Asian, as RET fusion-positive disease is more common.
- There are uncertainties concerning safety due to the lack of control group.
- There are no direct comparative data and indirect evidence is limited to docetaxel and nintedanib plus docetaxel only. The ITC and NMA conducted by the submitting company suggested that selpercatinib was superior to docetaxel and nintedanib plus docetaxel in terms of ORR, PFS and overall survival. However there are a number of limitations in the analyses including the complexity of methods and potential compounding of uncertainty. The populations were broader than the licensed indication for selpercatinib with respect to RET fusion status. It was not possible to adjust for RET status in the pseudo docetaxel control arm in the ORR analysis versus docetaxel and the comparator studies used in the NMA were not adjusted for RET status, limiting the generalisability of the indirect results to practice. There was heterogeneity across study populations in terms of baseline characteristics and previous treatments. These factors make the results highly uncertain.

EMA specific obligations

To confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive NSCLC, the marketing authorisation holder (MAH) should submit the final study report from the pivotal study LIBRETTO-001 (due by December 2023).

The MAH should also submit the clinical study report of the Phase 3 study J2G-MC-JZJC (LIBRETTO-431) comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with previously untreated, locally advanced or metastatic, RET-fusion-positive non-squamous NSCLC (due by October 2023).[2]

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 NSCLC is a rare type of lung cancer. It generally affects younger patients, who have never smoked, who may have family and caring responsibilities of their own. It is a devastating condition which is often diagnosed at a late stage when symptoms of breathlessness, pain, fatigue can be debilitating and difficult to manage and have a substantial negative impact on the quality of life of patients.
- There is an unmet need for effective and better tolerated, targeted treatment for this patient population. Selpercatinib offers the first targeted treatment for RET fusion positive NSCLC.
- In responders, selpercatinib may reduce symptom burden, which could improve the quality of life of patients, help them be more independent and reduce hospital visits. It would offer hope for patients and their families and may allow a return to a relatively normal life. It may potentially also increase survival.
- Selpercatinib has been associated with efficacy against CNS metastases and this may be important in allowing younger patients to drive and to work and remain independent.
- The oral formulation of selpercatinib is convenient for patients and their families reducing the need for hospital visits for administration of chemotherapy.
- Selpercatinib has a manageable side effect profile and was considered likely to be better tolerated than chemotherapy options.

Additional Patient and Carer Involvement

We received patient group submissions from the Roy Castle Lung Cancer Foundation and the Scottish Lung Cancer Nurses Forum. Roy Castle Lung Cancer Foundation is a registered charity and the Scottish Lung Cancer Nurses Forum is an unincorporated organisation. Roy Castle Lung Cancer Foundation has received 12.5% pharmaceutical company funding in the past two years, including from the submitting company. Scottish Lung Cancer Nurses Forum has received 100% pharmaceutical company funding in the past two years, with none from the submitting company. 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.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of selpercatinib compared to docetaxel monotherapy and to nintedanib plus docetaxel in adults with non-squamous RET fusion-positive NSCLC who have received one or more lines of prior platinum based chemotherapy (i.e. second line plus). SMC clinical experts confirmed these are relevant comparators, although immunotherapies not used at first line could potentially be considered comparators at second line in a small number of patients.

The economic analysis used a standard partitioned survival model with three health states (progression free, progressed and death). The model had a weekly cycle and a lifetime horizon of 25 years. The clinical data source used in the economic analysis for selpercatinib was the Integrated Analysis Set population of the LIBRETTO-001 study at December 2019 cut-off (N=184). For the comparison with docetaxel a pseudo-control reference arm was created using the LIBRETTO-001 study data for selpercatinib and REVEL study for docetaxel and applying a time acceleration factor and propensity score matching with multivariate regression. A comparison with nintedanib + docetaxel was performed using the results of a published NMA to generate hazard ratios (HRs) for PFS and overall survival versus the reference arm. Choice of function for extrapolation of PFS and overall survival was performed by fitting a stratified Gompertz to the selpercatinib and docetaxel reference arm data for PFS and spline with knot=1 function for overall survival, with these functions chosen based largely on clinical plausibility. The HRs for nintedanib + docetaxel were applied to the reference arm PFS and overall survival estimates assuming proportional hazards for extrapolation. Alternative parametric functions were applied in scenario analysis.

Grade ≥3 AEs with at least 2% difference between selpercatinib and comparators were included in the economic analysis for costs and disutilities, based on data from LIBRETTO-001, REVEL (docetaxel) and LUME-Lung-1 (nintedanib+docetaxel) studies.

Utility values were applied by health state based on estimates used in previous NICE and SMC health technology assessments (HTA), with values from NICE TA484 in previously treated non-squamous NSCLC used in the base case as a proxy for second line plus RET fusion positive NSCLC (0.713 for progression free, 0.569 for progressed). AE disutilities were derived from HTA submission sources, with variable durations of approximately two to over three weeks assumed.

Costs included medicine acquisition and administration costs, monitoring costs (including ECG monitoring for patients treated with selpercatinib), health state costs, AE management and end of life palliative costs. Selpercatinib medicine costs accounted for different dose proportions and reductions over the course of treatment based on the LIBRETTO-001 study, and the same dose intensity assumed for the comparators. Selpercatinib and nintedanib are administered orally hence pharmacy time was included for dispensing, and other HTA sources used for IV administration time for docetaxel, with medicines wastage accounted for. Time on treatment was assumed to be equivalent to PFS plus an additional period based on the mean time from progression to discontinuation in the LIBRETTO-001 study. Time on treatment for comparators

was aligned with PFS, and capped at a maximum number of cycles according to defined schedules. Monitoring, subsequent treatments and health state resource use costs were based on estimates used in prior NICE HTAs in NSCLC. A cost was also included for the RET fusion portion of a multi-gene testing next generation sequencing (NGS) panel, estimated from NHS England and NHS Improvement applied as part of the ongoing NICE appraisal of selpercatinib, then applied to the positive test rate for each population to derive a cost per RET fusion-positive patient identified.

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 discount was offered on the list price of selpercatinib. A PAS discount is in place for nintedanib and this was included in the results used for decision-making by using estimates of the comparator PAS price.

In the comparison versus nintedanib plus docetaxel, SMC is unable to present the results provided by the company which used an estimate of the PAS price for nintedanib due to commercial confidentiality and competition law issues. Additionally, the submitting company has indicated that results at list prices for this comparison are also commercial in confidence and as such, no ICERs are presented for this comparison.

In the base case for selpercatinib versus docetaxel, the incremental cost-effectiveness ratio (ICER) is estimated with PAS at £72,710 per quality-adjusted life-year (QALY). The main driver of incremental costs was additional medicine acquisition costs for selpercatinib. Disaggregated base case results also showed that the majority of incremental costs and also incremental QALYs for selpercatinib were incurred in the progression free health state.

In one way sensitivity analysis, the ICERs were most sensitive to varying progression free health state utilities, and discount rates for outcomes. In scenario analysis ICER sensitivity was associated with alternative choices of parametric function for extrapolation of overall survival outcomes, with the exponential function producing the lowest ICERs, and the stratified Weibull the lowest relative survival benefits for selpercatinib and hence highest ICERs (Table 2). The use of the spline with knot=1 function for PFS extrapolation had a large impact on increasing the ICERs versus each comparator (Table 2). The impact of using alternative published HTA utility sources, and setting ToT to PFS, and assuming no diagnostic testing costs were also explored in scenario analysis (Table 2).

Table 2: Key sensitivity and scenario analysis results selpercatinib versus docetaxel, with PAS

	Sensitivity/scenario analysis	**Selpercatinib versus docetaxel ICER with PAS (cost/QALY)**
	Base case	£72,710
1	OS extrapolation - exponential	£58,108
2	OS extrapolation – stratified Weibull	£77,075
3	PFS extrapolation – spline knot=1	£81,742
4A	Alternative Utilities from NICE TA310 & TA252 (PFS: 0.672, PD: 0.473)	£80,382
4B	Alternative utilities from Libretto	£66,270

5	ToT equal to PFS curve selpercatinib	£68,635
6	ToT beyond progression using 95% CI	£67,602-£78,792
7	No diagnostic testing costs	£71,112
8	Increased £200 cost of NGS diagnostic testing	£80,509
9	20 year time horizon	£72,919

The economic analysis was associated with a number of limitations and uncertainties:

- The clinical evidence for selpercatinib consists of a single arm trial and consequently there is an absence of head-to-head clinical data versus relevant comparators. The indirect comparison conducted to estimate relative PFS and overall survival outcomes with docetaxel and nintedanib plus docetaxel has limits in robustness, as summarised in the clinical effectiveness section above, and in plausibility of outcomes estimated. The PFS and overall survival extrapolations and outcomes were highly uncertain and final base case estimates selected relied heavily on clinical expert opinion (e.g. overall survival estimates for the comparators were stated to be overestimated through the indirect comparison approach used so was adjusted using clinical expert opinion). Hence, the magnitude of any survival benefit for selpercatinib over the comparators is highly uncertain. The addition of nintedanib with docetaxel is estimated to only produce a small additional survival benefit based on applying HRs to the docetaxel reference arm derived from a large published NMA that has low generalisability to the target patient population. Hence, the overall survival estimates for comparators may lack face validity, compounded by the immaturity of the overall survival data from LIBRETTO-001.
- A mapping from EORTC QLQ-C30 data in LIBRETTO-001 to EQ 5D did not provide plausible health state utility estimates. Therefore, the health state utility estimates used in the economic analysis are based on previously published HTAs in other NSCLC patient populations, hence their relevance to the target RET fusion-positive population are uncertain. However, the utilities used in the base case seem to have reasonable face validity and uncertainty in the utilities used was explored in scenario/ sensitivity analysis with some impact on the ICERs (Table 2).
- Time on treatment with selpercatinib is uncertain, in particular the duration of treatment after disease progression that affects medicine costs in the economic model. A scenario assuming no treatment beyond progression has been explored, which decreases the ICERs, with an additional scenario exploring the impact on the ICER when ToT is varied by the ToT 95% confidence interval from LIBRETTO-001, which had a moderate impact on the ICER (Table 2). However, the company noted that while treatment beyond progression was an option in LIBRETTO and assumed within the model, the Summary of Product Characteristics (SPC) for selpercatinib does not recommend treatment beyond progression and thus extended treatment (and thus costs) may not arise in clinical practice.
- The base case ICERs with PAS for both comparisons are high, with potentially high upward ICER uncertainty related to overall survival /PFS and cumulative parameter uncertainty.

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 was unable to accept selpercatinib for use in NHSScotland.

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

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published Management of lung cancer: A national clinical guideline (SIGN 137) in 2014.[5]

The European Society for Medical Oncology (ESMO) published an updated version of Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up in September 2020.[6, 7]

The guidance makes the following recommendations for first-line treatment regardless of PD-L1 status:

- Chemotherapy with platinum doublets should be considered in all stage IV NSCLC patients without an actionable oncogenic driver, without major comorbidities and PS 0–2
- Carboplatin plus nab-paclitaxel may considered an option in advanced NSCLC patients, particularly in patients with greater risk of neurotoxicity, pre-existing hypersensitivity to paclitaxel or contraindications for standard paclitaxel premedication
- platinum-based chemotherapy plus PD-(L1) inhibitors have reproducibly demonstrated superiority to standard platinum-based chemotherapy and in the absence of contraindications may be preferred to platinum-based chemotherapy in patients with PS 0 or1 and PD-L1 < 50%
- Nivolumab plus ipilimumab represents an optional treatment regimen for patients with NSCLC

The following recommendations are made for second-line treatment:

- platinum-based chemotherapy is recommended as second-line treatment option in patients with progression after first-line immunotherapy with pembrolizumab
- PD-L1 and PD-1 inhibitors (nivolumab, pembrolizumab and atezolizumab) are the treatment of choice for most patients with advanced, previously treated, PD-L1-naive NSCLC, irrespective of PD-L1 expression; nivolumab is recommended in both squamous and non-squamous NSCLC; pembrolizumab is recommended in patients with previously treated NSCLC with PD-L1 expression > 1%; atezolizumab is recommended in patients with advanced NSCLC previously treated with one or two prior lines of chemotherapy
- in patients not suitable for immunotherapy, second-line chemotherapy is recommended. Comparable options as second-line therapy consist of docetaxel, or nintedanib plus docetaxel in patients with adenocarcinoma progressing after previous chemotherapy or immunotherapy

The September 2020 update also notes that targeting RET (while evidence of benefit is stronger) is not currently routinely recommended and recruitment into open trials is encouraged. Selpercatinib and pralsetinib showed preliminary strong efficacy in RET-fusion NSCLC.

The National Institute for Health and Care Excellence (NICE) published Lung cancer: diagnosis and management (NG 122) in March 2019.[8]

These guidelines predate the availability of selpercatinib and the SIGN guideline predates immunotherapy.

Additional information: comparators

Second-line and subsequent treatment depends on previous treatment and may include docetaxel, nintedanib, pemetrexed or immunotherapy.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per cycle/course/year (£)
Selpercatinib	**120 or 160mg orally twice daily**	**85,176 to 113,568**

Costs from Dictionary of Medicines and Devices Browser on 1 June 2021. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 5 patients eligible for treatment with selpercatinib in year 1 and 10 patients in year 5 to which confidential estimates of treatment uptake were applied.

Without PAS

The gross medicines budget impact was estimated to be £234k in year 1 rising to £1.35m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £208k in year 1 and £1.27m in year 5.

These estimates do not take account of any patient access schemes applied to displaced medicines.

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

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8. National Institute for Health and Care Excellence. Lung cancer: diagnosis and management. NICE guideline 122. Available at: https://www.nice.org.uk/guidance/ng122. 2019.

This assessment is based on data submitted by the applicant company up to and including 16 July 2021.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.