Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2867

lorlatinib film coated tablets (Lorviqua®)

Pfizer Limited

07 August 2026

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 reassessment under the end of life medicine process

lorlatinib (Lorviqua®) is accepted for use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after prior treatment with an ALK inhibitor.

In the relevant subgroup of a non-comparative phase I/II study of previously treated patients with ALK-positive advanced NSCLC, lorlatinib was associated with an objective response rate of approximately 40%. This was supported by results of a phase IV, post-approval study in a larger population, in which response rates were consistent with those observed in the phase I/II study.

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 previously accepted lorlatinib for use in this indication on an interim basis (SMC2239). This supersedes that advice.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Lorlatinib is a third-generation inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) tyrosine kinases. It crosses the blood-brain barrier and has broad-spectrum potency against multiple ALK kinase domain resistance mutations that can develop during treatment with existing first-generation and second-generation ALK tyrosine kinase inhibitors (TKIs).[1, 2]

The recommended dose is 100 mg orally once daily. Treatment with lorlatinib is recommended as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity. See the summary of product characteristics for further details.[1]

Since March 2020, lorlatinib has been available in NHSScotland as monotherapy for the treatment of adult patients with ALK-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK TKI therapy; or crizotinib and at least one other ALK TKI, on an interim basis subject to ongoing evaluation and future reassessment (SMC2239). This submission supports a reassessment following further data collection for the updated licensed indication of lorlatinib as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after prior treatment with an ALK inhibitor.[1]

Lorlatinib is accepted for use within NHSScotland as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor (SMC2415).

1.2. Disease background

NSCLC accounts for approximately 85% to 90% of lung cancers, with ALK-positive NSCLC making up approximately 4 to 5% of NSCLC patients. ALK tyrosine kinase is primarily involved in developmental processes and expressed at low levels in adults. ALK gene rearrangements are most commonly reported in patients with adenocarcinoma histology, never smokers, and those with wild-type epidermal growth factor receptor (EGFR) and Kirsten Rat Sarcoma (KRAS) genes. Important prognostic factors include: nodal involvement, size of primary tumour, baseline pulmonary function, gender, presence or absence of significant weight loss, and performance status. The brain is a common site of metastases in ALK-positive NSCLC and is associated with poor prognosis.[3]

1.3. Treatment pathway and relevant comparators

ALK inhibitors are the first-line treatment option for ALK-positive advanced NSCLC. The third-generation ALK inhibitor, lorlatinib (SMC2415), or the second-generation ALK inhibitors, alectinib (SMC2012) or brigatinib (SMC2314), are the preferred first-line treatments in Scotland. The first-generation ALK inhibitor, crizotinib may also be used first-line (SMC1152/16).[4]

First and second-generation ALK inhibitors are associated with the development of drug-resistant mutations, which can lead to disease progression. In patients who have progressed after first-line treatment, treatment options include platinum doublet chemotherapy with carboplatin and pemetrexed or an alternative ALK inhibitor. Lorlatinib was previously accepted for use by SMC on

an interim basis subject to ongoing evaluation and reassessment. At that time, the marketing authorisation restricted use to after treatment with alectinib or ceritinib, or after crizotinib and at least one other ALK TKI (SMC2239). The submitting company consider that chemotherapy, typically platinum doublet chemotherapy containing pemetrexed with cisplatin or carboplatin, is the relevant comparator for this reassessment, in patients whose disease has progressed after prior treatment with an ALK inhibitor.

1.4. Category for decision-making process

Eligibility for a PACE meeting

Lorlatinib meets SMC end of life 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 lorlatinib is from Study 1001 as detailed in Table 2.1.

Table 2.1. Overview of relevant study

Criteria	Study 1001 [2, 3]
Study design	Multicentre, open-label, single-arm, phase I to II study
Eligible patients	• Metastatic stage IV NSCLC (histologically or cytologically confirmed) that carried either a locally determined ALK or ROS1 gene rearrangement. • At least one measurable target extracranial lesion as per RECIST version 1.1. • Asymptomatic CNS metastases, with or without prior treatment. • Adequate bone marrow, liver, pancreatic and renal function. • ECOG performance status of 0, 1 or 2. Patients were assigned to expansion cohorts (EXP) based on their ALK or ROS1 mutation status and prior treatments for NSCLC. The relevant expansion cohorts were patients with ALK-positive advanced NSCLC with disease progression following: • EXP-2: previous crizotinib only. • EXP-3A: previous crizotinib and one or two regimens of chemotherapy given before or after crizotinib. • EXP-3B: one previous non-crizotinib ALK TKI (alectinib, brigatinib, or ceritinib) with any number of chemotherapy regimens. • EXP-4 and EXP-5: two (EXP-4) or three (EXP-5) previous ALK-TKIs with any number of prior chemotherapy regimens.
Treatments	Lorlatinib 100 mg orally once daily continuously in 21-day cycles. Treatment continued until investigator-assessed disease progression, unacceptable toxicity, withdrawal of consent, or death. Treatment could continue after objective progression on treatment if there was evidence of clinical benefit as per investigator.
Randomisation	There was no randomisation in Study 1001.
Primary outcome	There were two co-primary outcomes, assessed by ICR per RECIST version 1.1: • Objective tumour response (defined as a confirmed complete or partial response) • Intracranial tumour response
Key secondary outcomes	• Time to tumour response (defined as time from first dose to objective tumour response) • Duration of response (defined as time from first objective tumour response to disease progression or death from any cause) • PFS (defined as time from first dose to objective disease progression or to death due to any cause) • OS (defined as time from first dose to death due to any cause)
Statistical	The study did not include formal hypothesis testing; therefore, all results are descriptive only.

analysis	The analyses of EXP-3B to 5 were conducted post hoc.

Abbreviations: ALK = anaplastic lymphoma kinase; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; EXP = expansion cohort; ICR = independent central review; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; ROS1 = c-ros oncogene 1; TKI = tyrosine kinase inhibitor.

The results demonstrated an overall objective response rate (ORR) of 40% in the pooled EXP-3B to EXP-5 subgroup, the subgroup most relevant to the licensed indication. The intracranial response in this subgroup was 54%. [3] Detailed results are presented in Table 2.2.

Table 2.2. Results of the updated analyses of the co-primary outcomes of Study 1001 based on independent central review (data cut off 02 February 2018). [3]

	EXP-3B	EXP-4 and 5	EXP-3B to 5 (pooled)
Overall responses	n=28	n=111	n=139
Confirmed objective response (95% CI)	43% (24% to 63%)	39%, (30% to 49%)	40% (32 to 49%)
Complete response	3.6%	1.8%	2.2%
Partial response	39%	37%	38%
Intracranial responses [a]	n=9	n=48	n=57
Confirmed objective response (95% CI)	67% (30% to 92%)	52% (37% to 67%)	54% (41% to 68%)
Complete response	22%	21%	21%
Partial response	44%	31%	33%

Abbreviations: CI = confidence interval.

[a] number of patients with at least one measurable CNS lesion at baseline.

An analysis of response disagreement between independent central review (ICR) and investigator assessment reported overall response disagreement rates of 19%, 23% and 13% for EXP-3B, EXP-4 and EXP-5 respectively, with higher response rates reported for ICR. The intracranial response disagreement rates, for the same groups were 27%, 29% and 25% respectively.[3]

The results of secondary outcomes were supportive of the co-primary outcomes. For the pooled EXP-3B to EXP-5 group median time to tumour response was the same (1.4 months) in the intracranial group and the overall group. Median duration of intracranial response was 12.4 months.[3] For this reassessment, the submitting company presented results from the final overall survival (OS) analysis of Study 1001, with a median OS follow-up of 66.7 months in EXP-3B, -4 and -5.[5] See Table 2.3 for progression-free survival (PFS) and OS results.

Table 2.3. Results of the updated analyses of selected secondary outcomes of Study 1001 based on independent central review. [3, 5]

		EXP-3B	EXP-4 and 5	EXP-3B to EXP5 (pooled)
		n=28	n=111	n=139
Progression-free survival (data cut off 02 February 2018)	Number of events, n	20	77	97
	Median PFS, months (95% CI)	5.5 (2.9 to 8.2)	6.9 (5.4 to 9.5)	6.9 (5.4 to 8.2)
	KM estimated PFS at 12	27%	33%	32%

	months			
Overall survival (data cut off 27 July 2023)	Number of deaths, n	15	84	99
	Median OS, months (95% CI)	37.4 (12.3 to NR)	19.2 (15.4 to 30.2)	20.7 (16.1 to 30.3)
	KM estimated OS at 5 years	45%	23%	27%

Abbreviations: CI = confidence interval; KM = Kaplan-Meier; NR = not reached; PFS = progression-free survival; OS = overall survival.

2.2. Health-related quality of life outcomes

European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaires (EORTC QLQ) C-30 and lung cancer (LC)-13 were used to evaluate health-related quality of life in patients treated with lorlatinib. The LC13 questionnaire evaluates 13 typical symptoms of lung cancer patients, including coughing, pain, dyspnoea, sore mouth, peripheral neuropathy and hair loss.[6] For functioning, symptom and global quality of life (QoL) domains scores were categorised as improved, worsening or stable. For the Global QoL domain of QLQ-C30 approximately 43% of patients improved and 40% were stable during treatment. For both QLQ-C30 and LC13 a greater proportion of patients improved rather than worsened for most symptoms, with the exceptions of sore mouth, alopecia and peripheral neuropathy.[3]

2.3. Supportive studies

For this reassessment, the submitting company presented results from a phase IV, open-label, post-approval study (B7461027) in patients with ALK-positive metastatic NSCLC who had progressed on first line alectinib or ceritinib. This study was required as part of the conditional marketing authorisation specific obligations and was designed to substantiate the clinical efficacy in the EXP-3B cohort from Study 1001. Patients received lorlatinib 100 mg orally once daily in 21-day cycles. Participants continued to receive study treatment until objective disease progression, unacceptable toxicity, participant refusal, lost to follow-up or death, whichever occurred first.[7-9]

The primary outcome was confirmed ORR by ICR assessed by RECIST v1.1. Secondary outcomes included duration of response, PFS and intracranial ORR, all assessed by ICR. Of the 71 patients treated with lorlatinib, 85% had received alectinib and 15% had received ceritinib as prior ALK TKI. The median duration of lorlatinib treatment was 9.7 months (range 0.3 to 42.8 months). The study met its primary endpoint as the lower limit of the 95% CI around the estimated ORR exceeded 30%. The ORR was 46% in patients who had received prior ceritinib and 42% in those who had prior alectinib. The regulator considered that the ORR was consistent with that observed in the EXP-3B cohort of Study 1001 (43%). These data were considered to support the efficacy of lorlatinib in patients previously treated with a second-generation ALK inhibitor with a reasonable sample size.[7-9]

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

In the absence of direct evidence comparing lorlatinib with relevant comparators, the submitting company presented two unanchored matching adjusted indirect comparisons (MAICs). The MAICs compared lorlatinib with single-agent or unspecified chemotherapy, as a proxy for platinum doublet chemotherapy. The MAIC populations were adult patients with ALK-positive advanced NSCLC whose disease has progressed after a second or later lines of therapy, following prior

treatment with one or two ALK TKI therapies. Separate MAICs were conducted for PFS and OS. The comparative PFS and OS estimates derived from the MAICs were used in the sensitivity analyses of the economic evaluation. See Table 2.4 for further details.

Table 2.4: Summary of indirect treatment comparison

Criteria	Overview
Design	Unanchored matching adjusted indirect treatment comparisons.
Population	Two matching cohorts from Study 1001; patients relapsing after crizotinib plus one or two lines of chemotherapy receiving lorlatinib (cohort EXP-2 to 3A) and patients relapsing after one non-crizotinib ALK TKI or crizotinib and another ALK TKI with or without any number of previous chemotherapy regimens receiving lorlatinib (cohort EXP-3B to 5).
Comparators	Single-agent chemotherapy (pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2 every 3 weeks) from the ALUR and ASCEND-5 studies and unspecified chemotherapy from the PROFILE 1001/1005 studies.
Studies included	ALUR[10, 11] and ASCEND-5[12] (for chemotherapy PFS data), and PROFILE 1001/1005[13] (for chemotherapy OS data).
Outcomes	PFS and OS.
Results	In both MAICs, the point estimates of the results favoured lorlatinib. As the 95% confidence intervals for the HRs do not cross 1 this suggests there was evidence of statistically significant differences between treatments.

Abbreviations: ALK = anaplastic lymphoma kinase; CI = confidence interval; HR = hazard ratio; MAIC = matching adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

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

3. Summary of Safety Evidence

Evidence from Study 1001 supports the safety of lorlatinib for the treatment of patients with ALK-positive advanced NSCLC. However, there are no comparative safety data available. The safety analysis set of both the phase I and II parts of Study 1001 included all patients who received at least one dose of lorlatinib 100 mg (n=295). All patients reported at least one adverse event and the majority were considered treatment related. The following treatment related adverse events were reported: hypercholesterolemia (84%), hypertriglyceridemia (67%), oedema (55%), peripheral neuropathy (48%), fatigue (28%), cognitive effects (29%), weight gain (26%), mood effects (23%), diarrhoea (23%) and vision disorders (15%). The most common grade 3 or 4 events were hypercholesterolemia or hypertriglyceridemia.[3]

Lorlatinib may cause multiple CNS effects which could have a negative impact on the patient's QoL.[3]

Overall, the safety profile of lorlatinib was considered to be tolerable and manageable. Longer-term safety data from the final OS analysis were generally consistent with those previously reported, although there was a slight increase in the frequency of some all-cause adverse events. In the phase IV study, the safety profile was consistent with Study 1001.[5, 7-9] Serum cholesterol, triglycerides, blood pressure and serum glucose should be monitored prior to initiation and regularly thereafter. Patients may require additional lipid lowering therapy. See the summary of product characteristics for further information.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- The results for Study 1001 co-primary outcomes, based on independent central review, demonstrated an overall ORR of 40% (56/139) in the study subgroup most relevant to the licensed indication (EXP-3B to 5). The intracranial response in patients with at least one CNS lesion at baseline in this subgroup was 54% (31/57) which indicates good CNS penetration.[2]
- This result was further supported by a median PFS of 6.9 months, and a median OS of 20.7 months in the final OS analysis, which was consistent with earlier analyses.[3, 7]
- The regulator considered that the benefit of lorlatinib following disease progression on other ALK inhibitors in terms of ORR, PFS and OS as clinically relevant and the stabilisation of CNS disease as highly clinically relevant in this patient population.[3]
- Phase IV data were considered to support the efficacy of lorlatinib in patients previously treated with a second-generation ALK inhibitor (alectinib or ceritinib) with a reasonable sample size.[8]

4.2. Key uncertainties

- Study 1001 is a single-arm study with no comparative data. The magnitude of any treatment effect is unknown in the absence of a control group.
- The submitting company concluded that the MAIC results showed that lorlatinib was associated with a statistically significant decrease in hazard compared with chemotherapy (pemetrexed or docetaxel) for both PFS and OS. The company did not update the MAICs with the final OS results from Study 1001; therefore, the impact on the relative treatment benefit remains unclear, although OS results were consistent between the interim and final analyses. The comparators were a proxy for platinum-based doublet chemotherapy. There are several methodological limitations, including differences in study design that could not be fully accounted for and an inability to adjust for all prognostic factors, introducing potential bias from unobserved confounders. The chemotherapy group from PROFILE 1001/1005 received unspecified regimens limiting external validity, and subsequent treatments were not reported, potentially confounding OS estimates. Given these limitations, the company's conclusions are uncertain.
- In the absence of randomisation and blinding, Study 1001 is at high risk of selection bias for all outcomes. Subjective patient reported outcomes such as those on health-related QoL and safety outcomes are at risk of performance and detection bias.[3]
- There was a high response disagreement rate for ORR, up to 23% and up to 29% for intracranial responses, between independent central review and study investigators. The regulator noted that these differences are likely to compromise the robustness of data.[3]
- The sample size for the Study 1001 subgroup most relevant to the indication under review (EXP-3B to 5) was limited (n=139). Additionally, it is uncertain if Study 1001 results are likely to represent results in the Scottish population: approximately 38% of patients were Asian and smoking status was not recorded.

- Cohorts EXP2 and EXP3A of Study 1001 may be relevant to the now broader licensed indication; however, data from these cohorts were not included in this reassessment (excluding the MAICs). Cancer Medicines Outcome Programme Public Health Scotland (CMOP-PHS) data indicate that most patients (70%) received a non-crizotinib ALK inhibitor prior to lorlatinib (including alectinib, brigatinib or ceritinib).[14] This suggests that the EXP-3B to 5 cohort may better reflect the Scottish population than the EXP2 and 3A cohorts.

4.3. Clinical expert input

SMC clinical experts advised that lorlatinib is the preferred first-line treatment due to CNS penetration. They considered that lorlatinib offers an effective second-line treatment option in patients who have progressed on alternative first-line ALK TKI treatments and is used in preference to chemotherapy for those patients, since interim acceptance.

4.4. Service implications

No substantial service implications are expected.

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 lorlatinib as an end of life medicine in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- ALK-positive advanced NSCLC is a severe, life-threatening condition with substantial physical, psychological, social and financial impact. There is a significant risk of brain metastases and symptoms such as breathlessness, chronic cough, fatigue, weight loss, reduced appetite and pain can be difficult to control and may restrict mobility, independence, work, caring responsibilities and family life. It particularly effects young women, who may have children, be working or care for relatives.

- Lorlatinib is already available in NHSScotland for patients with ALK-positive advanced for patients who have progressed after prior treatment with an ALK inhibitor following interim acceptance and PACE participants supported its continued use in this setting.

- There is an important unmet need after progression on a prior ALK inhibitor. Other treatment options are limited, with chemotherapy often the main alternative; this is not targeted to the ALK mutation, response rates are low, it requires hospital-based infusion and may be associated with substantial side effects and reduced QoL.

- Lorlatinib offers a targeted oral treatment option that may delay progression, reduce treatment burden, and provide clinically meaningful disease control, including intracranial activity. Patients who have had access to lorlatinib have described substantial health-related benefits, including regained independence, being able to drive again, participate in hobbies

and spend more meaningful time with family. These benefits have improved QoL and reduced psychological distress for both patients and those close to them.

- Monitoring requirements include routine blood tests and dose modifications or interruptions may be required to manage adverse events. This is consistent with current practice for ALK inhibitors, and lorlatinib is already used within NHSScotland oncology services therefore no substantial service implications are expected.

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 10% 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

An economic case was provided by the submitting company. This is summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	Lifetime time horizon of 20 years.
Population	Patients with ALK-positive advanced NSCLC whose disease has progressed after prior treatment with an ALK inhibitor.
Comparators	Platinum doublet chemotherapy. This comprised pemetrexed with cisplatin or carboplatin.
Model description	Three-state partitioned survival model with three health states (pre- progression, post-progression and death).
Clinical data	The clinical data for lorlatinib were taken from the single-arm phase II study 1001, which informed the patient baseline characteristics (age, weight, gender), PFS and overall survival , treatment duration, and adverse events.[2, 3] The relevant clinical studies identified for the treatment effect parameters for platinum doublet chemotherapy included: ALUR, ASCEND-5, and PROFILE 1001/1005.[10-13] These studies were in single agent and unspecified chemotherapy and were used as a proxy for platinum doublet chemotherapy. ALUR and ASCEND-5 were used to provide evidence for PFS while a retrospective analysis of PROFILE 1001/1005 was used for OS estimates for platinum doublet therapy.
Extrapolation	Indirect treatment comparisons were required to enable a comparison with the platinum doublet chemotherapy proxy comparator evidence. The base case used a naïve comparison involving the fitting of independent parametric functions to the observed lorlatinib and chemotherapy data for PFS and OS independently. Lorlatinib OS and PFS were extrapolated using the generalised gamma function. Platinum doublet chemotherapy OS was extrapolated using the log-normal with PFS extrapolated using the log-logistic. An alternative approach using hazard ratios from the MAICs was considered in scenario analysis. Time on treatment for lorlatinib was assumed to be the same as PFS with some additional

	treatment duration to account for progressed patients who continue to receive lorlatinib. Treatment duration for platinum doublet chemotherapy was assumed the same as PFS or a maximum of 6 cycles.
Quality of life	Age-adjusted treatment-specific utility values were used for the progression-free health state. For lorlatinib the values were derived from mapping EORTC QLQ-30 data collected within the phase II part of Study 1001 to the EQ-5D-3L based on a published algorithm.[15, 16] For doublet chemotherapy, a value of 0.72 was used, derived from the PROFILE 1014 study of crizotinib versus platinum-based chemotherapy from SMC.[17] Post-progression utility was based on published sources, and in the base case estimated to be 0.65.[18]
Costs and resource use	Costs included medicine acquisition, medicine administration, health state monitoring, concomitant medication, subsequent therapies, treatment of adverse events, and terminal care.
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 discount was offered on the list price. A PAS discount is in place for pembrolizumab and atezolizumab and this was included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered, and descriptions of these key scenarios are provided in Table 6.3.

Table 6.3: Scenario analysis

	Parameter	**Base case**	**Scenario**
1	OS extrapolation	Lorlatinib: Gen gamma PDC: log-normal	Both exponential
2	PFS extrapolation	Lorlatinib: Gen gamma PDC: log-logistic	Both Gompertz
3a	Treatment waning (PFS + OS)	None	At 5 years
3b			At 3 years
4	Time horizon	20 years	10 years
5	PFS utility values	Lorlatinib: Study 1001 (0.785) PDC: SMC 1329/18 (0.720)	Both Study 1001 (0.785)
6	PD utility values	Labbe 2017 (0.650)	Zhou et al. [19] (0.59)
7	PDC ToT cap	6 cycles	4 cycles
8	Lorlatinib duration of treatment beyond progression	Base case 2.6 months	50% increase (4 months)
9a	Comparative efficacy OS and PFS	Independent curves and no population adjustment	MAIC, EXP-3B:5 HRs (OS = 0.43, PFS = 0.35)
9b			MAIC, EXP-3B:5 HRs x2
9c			MAIC, EXP-3B:5 HRs x0.5
9d			MAIC, EXP-3B:5 HRs 95% CI upper bound (OS = 0.60, PFS = 0.43)
9e			MAIC, EXP-3B:5 HRs 95% CI lower bound (OS = 0.27, PFS = 0.29)
9f			MAIC, EXP-2:3A HRs (OS= 0.16,

			PFS = 0.20)
10	Contract pricing	Included	Excluded

Abbreviations: CI = confidence interval; CIC= commercial in confidence; HR = hazard ratio; Incr. = incremental; MAIC = matching adjusted indirect comparison; OS = overall survival; PDC = platinum doublet chemotherapy; PD = progressed disease; PFS = progression-free survival; QALY = quality-adjusted life year; ToT = time on treatment.

6.4. Key strengths

- The use of a partitioned survival model was appropriate.
- A comprehensive selection of parameters was considered in one-way deterministic scenario analysis.

6.5. Key uncertainties

- Clinical evidence for lorlatinib in the economic evaluation was based on a single-arm, phase II study with small patient numbers, PFS and overall survival as secondary outcomes, and relatively immature overall survival data. Although the updated final analysis of Study 1001 showed consistent results with the earlier data cut off and increased the maturity of overall survival data, these data were not included in the economic evaluation. In addition, lorlatinib data from a phase IV study were also not included. Scenario analysis considered alternative OS and PFS extrapolation distributions to attempt to explore these issues (Scenarios 1 and 2).
- There were limitations in the clinical efficacy evidence for platinum doublet chemotherapy increasing uncertainty in the face validity of the model results. The comparator effectiveness was based on chemotherapy data that may not reflect platinum doublet chemotherapy, drew on different sources for PFS and OS, and relied on limited retrospective evidence for OS from systemic therapy (presumed to be chemotherapy).
- The base case approach consisted of a naïve comparison of lorlatinib and comparator chemotherapy with independent curves fitted to each dataset. Compared to a naïve comparison, the use of a MAIC has an advantage of adjusting for differences in patient characteristics. Using this approach assumes proportional hazards, which may not apply for the overall survival estimates. However, using the MAIC results for PFS and overall survival in the economic analysis with EXP-3B to 5 data resulted in an increased ICER (Scenario 9a). Due to limitations of the MAIC, including the weaknesses in the comparator data, further scenario analysis explored the impact of varying the hazard ratio inputs (Scenarios 9b to 9e).
- There was uncertainty over time on treatment estimates for lorlatinib, so it was assumed that time on treatment was equal to PFS which was uncertain. Hence the submitting company included some additional monthly costs of treatment with lorlatinib to account for treatment beyond progression. Exploring this in scenario analysis to increase the assumed duration increased the ICER (Scenario 8).
- In the revised indication and proposed position in the reassessment, as the prior ALK TKI's are not specified, this potentially increases the relevance of the EXP-2 and EXP-3A cohorts

from Study 1001. The submitting company noted that as second-generation ALK inhibitors are used to treat most patients they have replaced the use of crizotinib in the first line setting, reducing the relevance of the EXP-2 and EXP-3A cohorts. Based on PHS-CMOP data, this may be reasonable. Therefore, while the EXP-3B to 5 cohorts may remain the most relevant, there was no scenario analysis incorporating pooled data from the EXP-2, EXP-3A, and EXP-3B to 5 cohorts to fully explore this uncertainty.

- An area of uncertainty was the year of the cost sources used in the economic model, which were drawn from data available at the time of the original submission. While this is likely to have a limited impact on the economic results, the absence of updated costs weakens the economic case.
- The cost of pemetrexed, carboplatin, and cisplatin in NHS practice is lower than the price used in the economic model due to the existence of a national framework agreement for this medicine. Using the national framework contract price had a small upward impact on the cost-effectiveness results.

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

7. Conclusion

After considering all the available evidence and the output from the PACE process, the Committee accepted lorlatinib for use in NHSScotland.

8. Guidelines and Protocols

The National Institute for Health and Care Excellence (NICE) updated 'Lung cancer: diagnosis and management (NICE guideline 122)' in March 2024. [20]

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. [21]

ESMO published 'ESMO Oncogene-Addicted Metastatic Non-Small-Cell Lung Cancer Living Guideline, v1.3' in February 2026. [22]

9. Additional Information

9.1. Product availability date

06 May 2019

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28 days (£)
lorlatinib	**100 mg orally once daily**	**4,931**

Costs from BNF online on 30 April 2026. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 52 patients eligible for treatment with lorlatinib in each year. The estimated uptake rate was 42% in each year. This resulted in 21 patients estimated to receive treatment each year.

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.**

References

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This assessment is based on data submitted by the applicant company up to and including 12 June 2026.

**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 includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS 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. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees 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.