SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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alectinib 150mg hard capsules (Alecensa®) SMC2012
Roche Products Limited

6 July 2018

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

alectinib (Alecensa®) is accepted for use within NHS Scotland.

Indication under review: as monotherapy for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

Alectinib, compared with another tyrosine kinase inhibitor, significantly improved progression-free survival in treatment-naïve adults with advanced or recurrent ALK-positive NSCLC.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of alectinib. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Published 13 August 2018

Indication

As monotherapy for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).[1]

Dosing Information

Alectinib 600mg orally twice daily, swallowed whole with food. Treatment should be continued until disease progression or unacceptable toxicity. Dose changes to manage adverse events are detailed in summary of product characteristics.[1]

A validated ALK assay is necessary for the selection of ALK-positive NSCLC patients. ALK-positive NSCLC status should be established prior to initiation of alectinib therapy. Treatment with alectinib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.[1]

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Product availability date

December 2017

Alectinib received an Early Access to Medicines Scheme (EAMS) positive scientific opinion on 01 September 2017 for use as monotherapy for first-line treatment of adult patients with ALK-positive advanced NSCLC and this expired in December 2017.

Alectinib meets SMC ultra-orphan criteria.

Summary of evidence on comparative efficacy

Alectinib is a tyrosine kinase inhibitor (TKI) licensed for the treatment of advanced or recurrent ALK-positive NSCLC. Inhibition of ALK tyrosine kinase activity leads to induction of tumour cell death (apoptosis).[1] SMC has previously issued advice that alectinib is not recommended for use in patients with ALK-positive advanced NSCLC previously treated with crizotinib. This submission is for first-line use.

An open label phase III study (ALEX) recruited adults with previously untreated, advanced or recurrent ALK-positive NSCLC who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and measurable disease on Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Randomisation was stratified by ECOG performance status (0 or 1 versus 2), race (Asian versus non-Asian) and central nervous system (CNS) metastases at baseline (presence versus absence) and patients were equally assigned to receive alectinib 600mg orally twice daily or crizotinib 250mg orally twice daily. These were continued to disease progression or unacceptable toxicity. The primary outcome, investigator-assessed progression-free survival (PFS), was defined as the time from randomisation to date of first documented disease progression as determined by investigator using RECIST version 1.1 or death. This was evaluated in the intention-to-treat (ITT) population, which consisted of all randomised patients.[2,3]

At the primary data cut-off (9 February 2017), after a median follow up of 18.6 and 17.6 months in the alectinib and crizotinib groups, respectively, 41% (62/152) and 68% (102/151) of patients had disease

progression or had died. The primary outcome, investigator-assessed PFS, was significantly greater with alectinib compared with crizotinib, with a hazard ratio (HR) of 0.47 (95% confidence interval [CI]: 0.34 to 0.65); p<0.001. Median PFS was not reached with alectinib and was 11.1 months with crizotinib. There were consistent PFS results assessed by an independent review committee (IRC), with a HR of 0.50 (95% CI: 0.36 to 0.70), p<0.001, and median PFS of 25.7 versus 10.4 months in the respective groups. There was no significant difference between the groups in investigator-assessed objective response rate (ORR), defined as complete response (CR) or partial response (PR) on RECIST version 1.1: 83% (126/152) in the alectinib group versus 76% (114/151) in the crizotinib group. These were mainly PR, with CR achieved by six patients in the alectinib group and two patients in the crizotinib group. Duration of response was longer with alectinib than with crizotinib, with a HR of 0.36 (95% CI: 0.24 to 0.53). Median duration of response was not reached in the alectinib group and was 11.1 months in the crizotinib group. Overall survival (OS) data were immature as only 23% (35/152) and 26% (40/151) of patients in the respective groups had died. Also as the previous key secondary endpoint (investigator-assessed ORR) was not statistically significant, OS was not formally tested, but was associated with a HR of 0.76 (95% CI: 0.48 to 1.20). An analysis of OS is planned when approximately 50% of patients have died.[2,3]

In the alectinib and crizotinib groups: 12% (18/152) and 45% (68/151) of patients had a first progression event involving the CNS. Time to CNS progression was significantly longer with alectinib than with crizotinib, with a HR of 0.16 (95% CI: 0.10, 0.28), p<0.001. Significantly more patients achieved a CNS response on RECIST with alectinib, compared with crizotinib in the subgroup with measurable CNS lesions at baseline, 81% (17/21) versus 50% (11/22), and in the subgroup with measurable and non-measurable CNS metastases at baseline, 59% (38/64) versus 26% (15/58). Median duration of CNS response was longer with alectinib compared with crizotinib, 17.3 versus 5.5 months and not reached versus 3.7 months in the respective subgroups.[2,3]

Quality of life was assessed using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire−Core (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13). Analyses of EuroQoL 5 Dimension (EQ-5D) were exploratory.[3] The EUnetHTA report notes that there was no difference between the groups in time to deterioration (TTD) for global health score, HR 0.72 (95% CI: 0.38 to 1.39); cognitive function, HR 0.85 (95% CI: 0.55 to 1.33); cough; chest pain, fatigue, pain in other parts and dyspnoea.[5]

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

Summary of evidence on comparative safety

The safety profile of alectinib in first-line ALK-positive NSCLC is consistent with that in the second-line setting. Newly identified adverse events from the safety dataset submitted for the first-line indication include increased weight, acute kidney injury, dysgeusia and stomatitis.[2]

In the ALEX study median duration of treatment was longer in the alectinib group compared with the crizotinib group, 17.9 versus 10.7 months, although mean dose intensity was comparable between treatment arms, 96% and 92%, respectively. The rates of adverse events within the respective alectinib and crizotinib groups were 97% (147/152) and 97% (146/151), which were considered treatment related in 77% and 89%. Across the alectinib and crizotinib groups there was a lower rate of adverse events with severity of at least grade 3 for alectinib (41% versus 50%), however, there were similar rates of serious adverse events (28% and 29%). Adverse events with a fatal outcome (grade 5) occurred in 3.3% and 4.6% of patients, respectively. Rates of adverse events leading to discontinuation of treatment were similar across the treatment groups (11% and 13%). However, alectinib, compared with crizotinib,

had lower rates of adverse events leading to dose reduction (16% and 21%) and drug interruption (19% and 25%), respectively.[3]

In the ALEX study gastrointestinal adverse events were the most common and were reported by fewer patients in the alectinib group compared with the crizotinib group: nausea (14% versus 48%), diarrhoea (12% versus 45%) and vomiting (7.2% versus 38%). Other adverse events reported at a lower frequency with alectinib were elevations of alanine aminotransferase (ALT) (15% versus 30%), aspartate aminotransferase (AST) (14% versus 25%) and gamma-glutamyltransferase (0.7% versus 6.6%), peripheral oedema (17% versus 28%), dizziness (7.9% versus 14%), dysgeusia (2.6% versus 19%), alopecia (0.7% versus 7.3%), visual impairment (1.3% versus 12%), blurred vision (2.0% versus 7.3%) and photopsia (0 versus 6.0%). The following adverse events were reported more frequently with alectinib compared with crizotinib, increased blood bilirubin (15% versus 1.3%), increase in weight (10% versus 0%), myalgia (16% versus 2.0%), musculoskeletal pain (7.2% versus 2%), anaemia (20% versus 4.6%) and photosensitivity reaction (5.3% versus 0%).[3]

Summary of clinical effectiveness issues

Alectinib is the third TKI (after crizotinib and ceritinib) licensed for the first-line treatment of advanced or recurrent ALK-positive NSCLC.[1,6,7] For this indication, crizotinib has been accepted by SMC (advice number 1152/16) for use within NHS Scotland, however, SMC issued advice (number 1333/18) in April 2018 that ceritinib is not recommended for use within NHS Scotland due to non-submission. Alectinib meets SMC ultra-orphan criteria.

Approximately 5% of patients with NSCLC have the EML4 ALK fusion gene (resulting from chromosomal inversion at 2p21 and 2p23) which makes an ALK fusion protein that contributes to increased cell proliferation and survival in tumours expressing these genes. ALK positive tumours tend to be associated with younger patients, adenocarcinoma histology and history of never or light smoking, with relatively higher incidence in females. Advanced ALK-positive NSCLC has a high risk of CNS metastases and the CNS is the most common site for disease progression. There is substantial morbidity associated with CNS metastases, and their treatment. The current first-line treatment for advanced ALK positive NSCLC patients is a TKI, such as crizotinib. Although crizotinib significantly improved PFS compared with pemetrexed plus platinum-based chemotherapy, all patients relapse with disease progression on average within one year and the CNS as the primary site of progression in 46% of patients. Survival after relapse is poor and the presence of CNS metastases results in poor prognosis and shorter survival.[2,3]

In the pivotal phase III study (ALEX) alectinib significantly improved PFS compared with crizotinib, a standard first-line treatment for advanced or recurrent ALK-positive NSCLC, with a median increase of about 15 months in the IRC analysis. Alectinib, compared with crizotinib, was associated with benefits on CNS pathology as it significantly prolonged the time to CNS progression and in the subgroup of patients with CNS metastases at baseline, it was associated with higher rates of CNS response. These benefits may be particularly relevant in ALK-positive NSCLC, which is associated with high frequencies of CNS metastases. The European Medicines Agency (EMA) noted that the effect of alectinib on CNS metastases is compelling and of high clinical relevance. Alectinib may have benefits for patients in terms of tolerability compared with crizotinib as it associated with lower rates of adverse events affecting the gastrointestinal tract and vision, although it was associated with a higher rate of events in skeletal muscles.[2,3]

Limitations of the evidence base include the open-label design of the pivotal and supporting studies, which may affect reporting of subjective outcomes such as adverse events and quality-of-life. Also survival data from both studies are immature. Further overall survival analysis in the ALEX study is

planned when 50% of patients have died. However, this may be confounded by use of ALK inhibitors after disease progression in countries where these are available. Although data on CNS response in the ALEX study was noted to be from a limited number of patients (43 with measurable and 69 with non-measurable CNS metastases) it was considered clinically relevant by the EMA.[2,3]

The majority of patients in the ALEX study had stage IV disease (97% [293/303]), adenocarcinoma, (92% [279/303]), ECOG performance status of 0 or 1 (93% [283/303]) and were not currently active smokers (94% [286/303]). The evidence base is therefore limited in those with stage IIIB disease, histology other than adenocarcinoma, ECOG performance status of 2 and in active smokers. However, this may be of limited importance in practice where the majority of patients have adenocarcinoma and a history of never or light smoking. Pre-defined subgroup analysis of the primary outcome by smoking status and ECOG score indicated that in these very small subgroups (active smokers, n=17; and ECOG status of 2, n=20), there were wide confidence intervals around lower point estimates of relative benefit: i.e. HR of 1.16 (95% CI; 0.35 to 3.90) for active smokers and HR 0.74 (95% CI: 0.25 to 2.15) for ECOG status of 2. However, the small sample size of these subgroups do not support definitive conclusions. Other pre-defined subgroup analyses by age, sex, race, baseline CNS metastases and previous brain radiation were consistent with the primary outcome.[2,3]

Clinical experts consulted by SMC considered that alectinib is a therapeutic advancement due to its benefits in efficacy and tolerability relative to the current standard first-line treatment for advanced ALK-positive NSCLC. They note that alectinib may replace this in practice and that it would be used in accordance with its product licence. They consider that the introduction of this medicine would not have any substantial implications for service delivery.

In NHSScotland, patients who progress after crizotinib are managed with ceritinib. In previously treated patients, ceritinib is specifically licensed for use following crizotinib; the introduction of alectinib may have implications for current treatment pathways.

While alectinib meets SMC ultra-orphan criteria in this indication, the company did not request a Patient and Clinician Engagement (PACE) meeting to consider the added value of alectinib in the context of treatments currently available in NHS Scotland.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing alectinib with crizotinib for use as first-line treatment in adult patients with ALK-positive advanced NSCLC. SMC clinical experts have confirmed that crizotinib is standard of care for these patients in Scotland.

A partitioned survival model was used with 4 health states; PFS, post-progression survival with CNS metastasis, post-progression survival without CNS metastasis, and death. The partitioned survival modelling approach allows for PFS and overall survival to be modelled separately based on the study data and therefore removes the need for assumptions linking PFS and overall survival outcomes. The economic model also included CNS PFS in addition to PFS in order to support the structure of the economic model. A lifetime time horizon of 30 years was modelled.

The main source of the clinical evidence used in the model is the ALEX study. Data relating to PFS, post-progression survival (with and without CNS metastasis), overall survival and time on treatment were used. The clinical data from the ALEX study were extrapolated beyond the end of the study period over the model time horizon. For each event in the model (progression, CNS metastasis and death) different parametric survival models were estimated and goodness of fit statistics were used to assess the statistical fit to the observed data. Clinical opinion and plausibility of the survival estimates were also

considered. For PFS, the Kaplan-Meier data were used for the first 18 months, after which the tail of the curve was extrapolated using the exponential function. For CNS PFS (ie patients who are alive and have not yet developed CNS metastasis), the Gamma function was used and for overall survival the exponential function was selected. Based on the extrapolated data, the model estimated 52% and 44% of patients would be alive at 4 years in the alectinib and crizotinib arms respectively. At 15 years the proportions were 9% and 5%.

Health-related quality of life data were collected in the ALEX study using the EQ-5D and disease-specific EORTC QLQ-C30. Based on these data, utility values for PFS (0.814) and progressed disease (0.725) were estimated. The company noted that it was not possible to use the utility data for CNS progressed vs non-CNS progressed patients separately due to small patient numbers in the CNS progressed subgroup. Instead, the company identified two studies from the literature where the quality of life of NSCLC patients with brain metastases was explored. Based on these studies, a utility value of 0.52 was applied to patients who progressed with CNS metastases. Disutilities associated with adverse events were not included separately in the base case analysis, but were included in a sensitivity analysis and had minimal impact on the results.

The cost of treatment following discontinuation of alectinib or crizotinib was included and based on clinical opinion the medicine costs of ceritinib, crizotinib and chemotherapy were applied as second-line treatments. The company acknowledged there is some uncertainty surrounding the treatments patients would receive following alectinib and in the base case analysis it was assumed 60% of patients would receive crizotinib second-line and 40% would receive chemotherapy. In the crizotinib arm, it was assumed that 90% of patients receive ceritinib and 10% chemotherapy.

The model also includes an additional one-off cost associated with CNS progression. This is in addition to the post progression health state costs applied in the model which include costs of subsequent treatments. The additional one-off cost was applied when a patient progresses with CNS metastasis and was based on patients receiving an oral dose of corticosteroids and stereotactic radiosurgery (SRS). This resulted in a cost of around £20,000 being applied upon progression with CNS metastasis. Other costs included terminal care costs and the costs of treating adverse events.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. A PAS is in place for crizotinib and this was included in the results used for decision-making by using estimates of the comparator PAS price. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, as these are commercial in confidence only the without-PAS figures can be presented.

The base case results and key sensitivity analyses are summarised in the tables below.

Table 1: base case results using the list prices for alectinib and crizotinib

Alectinib vs crizotinib	**Incremental cost**	**Incremental QALYs**	**ICER**
List prices for all medicines			
Base case	£62,252	1.16	£53,963

Table 2: Key scenario analysis using the list prices for alectinib and crizotinib

Scenario	**ICER (list prices for alectinib and crizotinib)**
OS distribution – Weibull	£30,128
OS distribution – Gamma	£32,109
Alternative PPS utilities	£71,382
Alternative subsequent treatment assumption	£63,381
Definition of PFS event using RECIST only	£62,473

The results presented do not take account of the PAS for crizotinib or the PAS for alectinib but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for crizotinib due to commercial confidentiality and competition law issues.

It also worth noting that ceritinib was included in the model as a subsequent treatment and there is a PAS in place for ceritinib. However the results presented above use the list price for ceritinib as a simplifying assumption. As ceritinib is included as a subsequent treatment in the crizotinib arm only (and as such is a driver of the model), a sensitivity analysis was provided which includes an estimate of the PAS price for ceritinib. However SMC is also unable to present the results provided by the company which used an estimate of the PAS price for ceritinib due to commercial confidentiality and competition law issues.

There are a number of limitations with the analysis:

- The benefits of preventing or delaying CNS progression may have been overestimated in the model, which could bias the results in favour of alectinib as the ALEX study showed a lower rate of CNS progression for patients treated with alectinib. An analysis was provided which combined CNS and non-CNS progressed disease into one health state (ie assumes the same survival, costs and utility values regardless of the type of progression). This increased the ICER to £84k using the list prices for both alectinib and crizotinib.
- The utility value of patients in the CNS progression health state seems low relative to the non-CNS progression health state. The non-CNS progressed disease utility value was estimated using EQ-5D data collected in the ALEX study which included all patients, including those who experienced CNS progression. The company provided additional sensitivity analysis which used the same utility value for CNS and non-CNS progression (0.62) and this increased the ICER to £75k using the list prices for both alectinib and crizotinib.
- The one-off cost applied to patients moving into the CNS progression health state may have been overestimated. The company noted that the majority of patients receive whole-brain radiotherapy (WBRT) in practice but as there is evidence to show this treatment may not be beneficial in this patient group, it was assumed that all patients receive SRS which is associated with a much higher cost. The company provided additional sensitivity analysis which assumed 77% of patients would receive WBRT and 23% SRS and this increased the ICER to £57k using the list prices for both alectinib and crizotinib. The one-off cost associated with CNS progression used in the model was considered excessive and not reflective of clinical practice in Scotland.
- There is some uncertainty regarding the treatments patients would receive second-line following alectinib and crizotinib treatment. SMC clinical experts were asked to comment on the company's assumptions and responses were mixed. The results are relatively sensitive to varying the proportion of patients assumed to receive second-line TKI treatments.
- Additional sensitivity analysis was provided to further explore the survival modelling given the immaturity of the overall survival data from the ALEX study. Using the Kaplan Meier overall survival data until 20 months then fitting an exponential tail increased the ICER to £56k (using the list prices for both alectinib and crizotinib). Reducing the time horizon to 10 years had minimal impact on the results. A scenario analysis was also provided which combined a number of the key uncertainties.

In this analysis more conservative utility and cost data were used for the progressed disease health states, Kaplan Meier overall survival data were used until 18 months then extrapolated using an exponential tail, PFS events were defined using RECIST criteria only, and the time horizon was reduced to 15 years. This increased the ICER to £85k using the list prices for both alectinib and crizotinib.

The Committee also considered the benefits of alectinib in the context of the SMC decision modifiers that can be applied and agreed that as alectinib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and after application of the appropriate SMC modifiers, the Committee accepted alectinib for use in NHS Scotland.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- 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 6.1% pharmaceutical company funding in the past two years with none from the submitting company. The Scottish Lung Cancer Nurses Forum has received 80% pharmaceutical company funding in the past two years with none from the submitting company.
- Lung Cancer is the leading cause of cancer related mortality in the UK. This is due to lung cancer patients having an exceptionally poor prognosis. Late stage lung cancer has a range of impacts on daily living. Symptoms such as breathlessness, weight loss and chest pain can reduce patients' ability to carry out personal care, cook for themselves and contribute actively to family or business activities. Fatigue can also be a consequence of the illness and/or the treatment and can result in further limitation on daily living activities. The psychological impact of diagnosis and the limited treatment options can have a major impact on the well-being of patients.
- Patients with ALK-positive advanced NSCLC are at high risk of the cancer spreading to the brain. New evidence shows that alectinib crosses the blood/brain barrier and can have significant anti-tumour activity in ALK-positive patients with brain metastasis. The side effect profile of alectinib may be more manageable than crizotinib.
- Alectinib may allow patients to return to work, improve their fitness and generally feel like they can take part in life again. It offers an additional period of time in active treatment. Whilst additional months and years are not the same as a cure, for someone finding out they have end stage disease, this extra time is desperately needed, boosting their quality of life and that of their family.

Additional information: guidelines and protocols

In 2016 the European Society for Medical Oncology (ESMO) published clinical practice guidelines for metastatic NSCLC and these were updated in June 2017. The updated guidelines recommend that first-line treatment with crizotinib is the preferred treatment for ALK-rearranged NSCLC. They also recommend that any previously-treated patient with an ALK fusion should receive crizotinib second-line if it has not been previously administered. The guidelines note that crizotinib penetration into the CNS is negligible and this pharmacological limitation is relevant to treatment decisions taking account of the high propensity of ALK-rearranged NSCLC to metastasise to the brain. They recommend ceritinib for

patients with ALK-positive advanced NSCLC who progress on or are intolerant to crizotinib. The guidelines indicated that the results of the ongoing ALEX study are awaited.[8]

In 2014 the Scottish Intercollegiate Guidelines Network (SIGN) issued publication number 137: management of lung cancer. This recommends that in patients with advanced NSCLC who have sensitising EGFR mutation, first line single agent TKI should be offered. For those patients who have advanced disease, are performance status 0 or 1, have predominantly non-squamous NSCLC and are EGFR mutation negative, systemic anti-cancer therapy (SACT) with cisplatin and pemetrexed should be offered. Thereafter, all other patients with NSCLC should be offered SACT with cisplatin/carboplatin and a third generation agent (docetaxel, gemcitabine, paclitaxel or vinorelbine). The guidelines recommend four cycles of platinum-doublet SACT; it is not recommended that treatment extends beyond six cycles.[9]

Additional information: comparators

crizotinib

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
alectinib	**600mg orally twice daily**	**65,416**
crizotinib	250mg orally twice daily	56,893

Doses are for general comparison and do not imply therapeutic equivalence. Costs from Dictionary of Medicines and Devices on 2 May 2018. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The company estimated there would be 7 patients eligible for treatment in year 1 rising to 38 in year 5.

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.

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

References

1. Roche Products Limited. Summary of product characteristics for alectinib (Alecensa®), last updated 23 March 2018.

2. European Medicines Agency. European public assessment report for alectinib (Alecensa®), Committee for Medicinal Products for Human Use (CHMP) assessment, EMA/CHMP/833519/2017, 12 October 2017.

3. Peters S, Camidge DR, Shaw AT et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med 2017; 377(9): 829-38.

4. *Commercial in Confidence**

5. Dental and Pharmaceutical Benefits Agency (TLV), Main Association of Austrian Social Security Institutions (HVB), Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ). Rapid assessment on pharmaceutical technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment. Alectinib as monotherapy for the first -line treatment of adult patients with ALK-positive advanced non-small cell lung cancer. EUnetHTA Project ID: PTJA03. 2017.

6. Pfizer Limited. Summary of product characteristics for crizotinib (Xalkori®), last updated 20 February 2018.

7. Novartis Limited. Summary of product characteristics for ceritinib (Zykadia®), last updated 11 November 2017.

8. Novello S, Barlesi F, Califano R, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology. 2016; 27(suppl_5): v1-v27 plus update June 2017.

9. Scottish Intercollegiate Guidelines Network (SIGN). Publication number 137: Management of lung cancer, 2014.

This assessment is based on data submitted by the applicant company up to and including 15 June 2018.

**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_statements/Policy_Statements*

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 drug 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 NHS Scotland 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 NHS Scotland 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.