

**crizotinib 200mg and 250mg hard capsules (Xalkori®)**

**SMC No 1329/18**

**Pfizer Limited**

4 May 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 ultra-orphan medicine process

**crizotinib (Xalkori®)** is accepted for use within NHS Scotland.

**Indication under review:** treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC).

In a small, single arm, open-label, phase I study of patients with advanced ROS1-positive NSCLC, treatment with crizotinib resulted in an objective response in 70% of patients.

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

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

**Chairman**  
**Scottish Medicines Consortium**

## Indication

The treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC).

## Dosing Information

The recommended dose of crizotinib is 250mg twice daily taken continuously.

The capsules should be swallowed whole, preferably with water, and should not be crushed, dissolved or opened. They may be taken with or without food.

An accurate and validated assay for ROS1 is necessary for the selection of patients for treatment with crizotinib. ROS1-positive NSCLC status should be established prior to initiation of crizotinib therapy. Assessment should be performed by laboratories with demonstrated proficiency in the specific technology being utilised.<sup>1</sup>

Treatment with crizotinib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

## Product availability date

25 August 2016

Crizotinib meets SMC ultra-orphan criteria for this indication.

## Background

Crizotinib is a selective small-molecule inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase and its oncogenic variants: hepatocyte growth factor receptor (HGFR, c-Met) RTK; ROS1 (c-ros); and recepteur d'origine nantais (RON) RTK. ROS1-positive non-small cell lung cancer (NSCLC) is a molecularly-defined subgroup with an estimated prevalence of 1% to 2% of NSCLC. This sub-type is associated with patients of younger age, adenocarcinoma histology, and a never or light smoking history. Crizotinib is already licensed for the treatment of ALK-positive NSCLC.<sup>1,2</sup>

Crizotinib for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

## Nature of condition

ROS1-positive advanced NSCLC represents an additional molecular subgroup of lung cancer patients who might benefit from specific targeted therapy. Details on its natural history and clinical experience are limited and the European Medicines Agency (EMA) notes that data on the prognostic value of ROS1 positivity are sparse and difficult to interpret. In addition there are limited data on how patients with ROS1-positive disease respond to chemotherapy. According to current guidelines, in ROS1-positive, epidermal growth factor-receptor (EGFR)-negative cancers, the first-line treatment for patients with good performance status is a platinum-doublet regimen, the non-platinum agent determined by histology. In non-squamous cancers, which include adenocarcinoma (the histological sub-type in which ROS1 rearrangement is predominantly identified) pemetrexed is recommended to be used with platinum. In all other histological types the combination agents recommended are gemcitabine, docetaxel, paclitaxel or vinorelbine.<sup>3,4</sup> In NHS Scotland, patients with non-squamous

histology, the recommended first-line option is platinum plus pemetrexed for four cycles. In patients willing to take maintenance chemotherapy, pemetrexed would then be offered. Crizotinib is the first targeted therapy to be licensed for the treatment of ROS1-positive NSCLC in the UK. Clinical experts consulted by SMC considered that crizotinib is likely to be more effective than chemotherapy in this patient group and therefore has the potential to address an unmet need. Crizotinib meets SMC ultra-orphan criteria and it is noted that eligible patients have a short life expectancy.

A patient and clinician engagement (PACE) meeting was held to consider the added value of crizotinib in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to the fact that ROS1-positive NSCLC is a rare subtype of lung cancer. Compared with more common types of lung cancer, ROS1-positive disease may occur in younger patients who are non-smokers. Although clinical experience in patients with ROS1-positive NSCLC is limited, the median survival is expected to be around one year with chemotherapy.

Patients with lung cancer are often diagnosed with advanced disease when treatment options are limited. The symptoms of advanced disease, including breathlessness, weight loss, chest pain and fatigue, have a significant impact on daily living and the diagnosis of ROS1-positive NSCLC has a negative emotional and physical impact on the patient's quality of life.

## Impact of new technology

### Summary of evidence on comparative efficacy

The pivotal evidence for this indication comes from one, single-arm, open-label, phase I study (PROFILE 1001) in patients with advanced cancer. The study initially included a dose-escalation phase from which the maximum established dose was then assessed in expansion phases in different molecular types. This included an expansion phase in a cohort of 53 patients with ROS1-positive NSCLC. Initially, 50 patients were found to be ROS1-positive but a further three patients, found to be ALK-negative and subsequently ROS1-positive from the dose-escalation phase, were also included. Results have been published for the initial 50 patients.<sup>5</sup> However, the regulatory approval and the company submission is based on results for all 53 patients.<sup>1, 2</sup> Eligible patients were aged at least 18 years, had histologically confirmed advanced NSCLC with a ROS1 rearrangement and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0 (or RECIST v1.1 for the three ALK-negative patients who were retrospectively determined to be ROS1-positive). They also had Eastern Co-operative Oncology Group (ECOG) performance status of 0 to 2 and adequate organ function. All patients received open-label treatment with crizotinib 250mg orally twice daily until disease progression (according to RECIST criteria), clinical deterioration, unacceptable toxicity, study withdrawal or death. Study treatment could be continued beyond disease progression at the discretion of the investigator and approval of the company.<sup>2, 5</sup>

The primary outcome was objective response rate (ORR: including complete and partial responses) assessed by the investigator using RECIST criteria in the response evaluable population (all enrolled patients who received at least one dose of crizotinib, had adequate baseline disease assessment and had either at least one post-baseline disease assessment after at least six weeks or withdrew or had progressive disease or death). At the time of the data cut-off (30 November 2014), after a median follow-up of 25.4 months, an ORR was achieved by 70% (37/53) of patients. There were five complete (9.4%) and 32 partial responses (60%). A number of secondary outcomes were assessed and results are presented in table 1 below. At the time of the analysis, 30% (16/53) of patients had died and median overall survival had not been reached. The probability of survival at 6 months was estimated as 91% (95% CI: 79 to 96) and at 12 months as 79% (95%: 65 to 88).<sup>1, 2</sup>

**Table 1: Results from the ROS1-positive NSCLC expansion phase of the PROFILE 1001 study<sup>1, 2</sup>**

	<b>Crizotinib 250mg twice daily (n=53)</b>
<b>Primary outcome</b>	
Objective response rate	70% (37/53) (95% CI: 56% to 82%)
<b>Secondary outcomes</b>	
Disease control rate* at 8 weeks	87% (46/53) (95% CI: 75% to 94%)
Disease control rate* at 16 weeks	79% (42/53) (95% CI: 66% to 89%)
Duration of response, median (months)	Not reached (range 15.2 to not reached)
Progression-free survival, median (months)	19.3 (95% CI: 14.8 to not reached)
Overall survival, median (months)	Not reached

\*disease control rate = percentage of patients with a complete or partial response or stable disease according to RECIST.

CI=confidence interval

Results from a number of retrospective and prospective small supportive studies in patients with ROS1-positive NSCLC found similar response rates with crizotinib to the PROFILE 1001 study.<sup>2</sup>

#### **Summary of evidence on comparative safety**

As the ROS1 expansion phase of PROFILE 1001 was a single-arm study, there are no comparative safety data. In this study, an adverse event was reported in all 53 patients and these were considered treatment-related in 98% (52/53) of patients. Serious adverse events were reported in 42% of patients and these were treatment-related in 3.8%. Adverse events of grade 3 or 4 severity were reported in 53% of patients and 30% were treatment-related. Adverse events led to permanent discontinuation in 7.5% of patients. In addition, 45% of patients required temporary discontinuation and 11% required dose reduction due to adverse events.<sup>2</sup>

The most frequent adverse events, reported by at least 20% of patients, (all-cause [considered treatment-related]) were visual disorder (87% [85%]), nausea (59% [49%]), oedema (55% [45%]), vomiting (51% [38%]), diarrhoea (45% [42%]), constipation (43% [34%]), dizziness (40% [19%]), upper respiratory tract infection (40% [0%]), increased aminotransferases (36% [30%]), fatigue (32% [19%]), neuropathy (30% [9.4%]), dyspnoea (28% [1.9%]), rash (26% [13%]), bradycardia (26% [21%]), decreased appetite (25% [11%]), headache (25% [0]), abdominal pain (23% [5.7%]), dysgeusia (23% [19%]) and cough (21% [0]).

The safety profile of crizotinib in the 53 patients with ROS1-positive NSCLC in the PROFILE 1001 study was consistent with the established overall crizotinib safety profile.<sup>2</sup> The summary of product characteristics includes details of warnings on the risks of hepatotoxicity, interstitial lung disease/pneumonitis, QT interval prolongation, bradycardia, cardiac failure, neutropenia and leucopenia, gastrointestinal perforation, renal failure and visual disorders with crizotinib.<sup>1</sup>

#### **Summary of clinical effectiveness issues**

In the ROS1 expansion phase of the PROFILE 1001 study, the ORR with crizotinib was 70% and the EMA considered this to be outstanding. This was supported by results for the secondary outcome of median PFS of 19.3 months. Results for the duration of response and overall survival are currently immature but since the median duration of response had not been reached after a follow-up of more than two years, the EMA considered this to be meaningful.

The study had a number of limitations including the small number of patients (n=53) and the lack of data versus relevant comparators.

The primary outcome was ORR, which although acceptable for a phase I study, is not sufficient to demonstrate clinical benefit. Duration of response, PFS and overall survival were secondary outcomes and mature data are awaited. There was no assessment of quality of life. The EMA noted that the ORR results with crizotinib compared favourably with the responses achieved to prior chemotherapy in the 46 patients in PROFILE 1001 who had received previous treatment. In addition, the median time to progression was longer with crizotinib (19.8 months) than with last prior therapy (8.1 months).<sup>2</sup>

Although the study included patients who were previously untreated and those who were previously treated, the data for previously untreated are very limited and based on results in seven patients only. However, the EMA considered that there were no concerns on efficacy of first-line treatment with crizotinib based on pre-clinical and anti-tumour similarities between ROS1-positive and ALK-positive disease.<sup>2</sup>

The company indicated that the ROS1-positive NSCLC population is similar to the ALK-positive NSCLC population and has therefore included results from the PROFILE 1007 and 1014 studies in ALK-positive patients as supporting evidence versus chemotherapy. Although the patient characteristics (including smoking history) and disease histology (i.e. adenocarcinoma) appear similar in both populations, there were differences in the results achieved in the different populations. The ORR with crizotinib of 70% in ROS1-positive patients (PROFILE 1001) was similar to 65% and 74% achieved in previously treated and untreated patients respectively with ALK-positive disease (PROFILE 1007 and 1014). However, the median duration of response had not been reached (after a median follow-up of 25.4 months) in ROS1-positive patients and was 7.4 months and 11.3 months in ALK-positive patients respectively. Median PFS was 19.3 months, 7.7 months and 10.9 months respectively.<sup>2, 6, 7</sup> These differences indicate uncertainty in whether the results for the ALK-positive patients can be used as a proxy for ROS1-positive patients.

The introduction of crizotinib for ROS1-positive NSCLC would offer an oral targeted treatment in this population who would otherwise be managed by chemotherapy. An accurate and validated assay is necessary to identify patients with ROS1 rearrangement for crizotinib treatment. Patients are not routinely tested for ROS1 at present and further testing would have implications for the service. Clinical experts consulted by SMC considered that crizotinib offered a therapeutic advance due to expected improvements in response rates and safety profile compared with chemotherapy. They indicated that the place in therapy of crizotinib would be first-line.

At the PACE meeting, the clinicians noted that the evidence base in ROS1-positive disease is limited but indicated that crizotinib was associated with a good response rate, superior to that which might be expected from chemotherapy, and an encouraging progression free survival. The stabilisation of disease may delay disease progression and delay the need for chemotherapy. Tumour shrinkage may reduce disease symptoms and improve the general health and quality of life of treated patients. This may allow patients to live well for longer. The PACE meeting participants noted that crizotinib is the only targeted therapy available for the treatment of patients with ROS1-positive NSCLC. The majority of patients would otherwise be treated with chemotherapy and experience in patients with ALK-positive NSCLC suggests that crizotinib is better tolerated than chemotherapy.

## Patient and clinician engagement (PACE)

A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of crizotinib as an ultra-orphan medicine in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- ROS1-positive NSCLC is a rare subtype of advanced lung cancer. Patients are often diagnosed with advanced disease when symptoms such as breathlessness, weight loss, chest pain and fatigue have a significant impact on daily living.
- Crizotinib is the only available targeted therapy for this patient group.
- Limited evidence indicates that crizotinib is an effective treatment for patients with ROS1-positive disease. It is associated with a good response rate and delays disease progression which would be expected to allow patients to live well for longer and have a positive impact on quality of life.
- Use of crizotinib would be anticipated to delay the need for chemotherapy in patients with ROS1-positive disease.
- PACE participants highlighted the significant side effects associated with chemotherapy that can have a severe impact on patients and their families. As in the ALK-positive population, crizotinib is expected to be better tolerated than chemotherapy in the ROS1-positive population, allowing patients to live a more normal life for longer which may include the ability to continue to work and care for family.
- The availability of an effective and well-tolerated treatment option would be expected to reduce the psychological distress associated with this disease.
- In contrast the chemotherapy, crizotinib is administered orally, allowing patients to be treated at home and reducing the need for hospital visits.

### **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 6.1% pharmaceutical company funding in the past two years, including from the submitting company. The Scottish Lung Cancer Nurses Forum has received 80% pharmaceutical company funding in the past two years, including 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.

## Value for money

The submitting company presented two cost-utility analyses that evaluated crizotinib (twice daily recommended dose 250mg taken orally), as monotherapy for the treatment of first and subsequent line ROS1-positive NSCLC. In first line, the company modelled crizotinib versus pemetrexed in

combination with platinum chemotherapy, either carboplatin or cisplatin, with each given approximately equal weight. In subsequent line, the comparator was docetaxel.

The economic evaluation was based on a partitioned survival cost-effectiveness model, consisting of three states (pre-progression, post progression, and dead). Duration of therapy is determined by time to treatment failure (TTF) survival curves with the exception of docetaxel, which was assumed to be administered for a maximum of three model cycles (based on the median progression-free survival of 2.6 months observed in the PROFILE 1007 study). The time horizon for the analysis was 20 years.

The clinical study of crizotinib in ROS1-positive patients, PROFILE 1001, was a small single arm study with immature overall survival data. Crizotinib has previously been the subject of SMC reviews in ALK-positive NSCLC patients based on PROFILE 1014 (first line - SMC 1152/16), and PROFILE 1007 (subsequent line - SMC 865/13). Based on a claimed homology of ROS1-positive and ALK-positive the company primarily adopted the PROFILE 1014 and 1007 studies as proxies for the cost-effectiveness analysis in ROS1-positive first line and subsequent line patients respectively. The company also submitted analyses based on the PROFILE 1001 study (applied for both first and subsequent line).

The models' time to event functions were based on data from the proxy studies. For overall survival in first line and subsequent line the exponential distribution was selected based on goodness of fit criteria and credibility of projected time to event. Functions were fitted adjusting for baseline covariates in fully stratified analyses, i.e. entirely separate functions fitted for each arm for first line, with a hazard ratio applied to the docetaxel arm in subsequent line. Covariate patterns from UK real world setting were applied in the modelling. The rank preserving structural failure time (RPSFT) approach to adjustment for treatment switching was also employed.

For PFS in first line, lognormal and generalized gamma distributions were selected for crizotinib and pemetrexed plus platinum therapy, respectively, with the Weibull and lognormal distributions applied in the crizotinib and chemotherapy arms of the subsequent line model respectively. In order to model time on treatment (i.e. TTF) the economic evaluation extrapolated the available data using the exponential and Gompertz functions for crizotinib and pemetrexed plus platinum therapy respectively in the first line model, and the Weibull function was used for crizotinib in subsequent line.

PROFILE 1001 does not contain health related quality of life data and therefore the analysis proxies ROS1-positive patients' quality of life with EQ-5D-3L utility data from PROFILE 1014 and 1007. For PROFILE 1014 the pre-progression utility values were 0.81 and 0.72 for crizotinib and pemetrexed plus platinum therapy respectively. For PROFILE 1007, utility scores on treatment were reported as 0.82 for crizotinib and 0.66 for docetaxel monotherapy. The impact of adverse events is assumed to be reflected in the different utility estimates applied in each arm.

Following progression crizotinib patients who continued on therapy maintained the progression free quality of life weight. Patients no longer treated with crizotinib or who received pemetrexed plus platinum therapy were assumed to receive docetaxel monotherapy as a second-line treatment. The duration of docetaxel monotherapy treatment and the related quality of life weight was assumed to be equal to the median PFS and utility value for second-line docetaxel in PROFILE 1007. Following docetaxel, patients receive BSC for which a quality of life weight for progressive disease following second-line treatment was applied based on a published standard gamble based estimate.

Medicine acquisition costs were included in the analysis as well as health state (separated by pre and post-progression), adverse event, and ROS1-positive testing costs. Health state costs reflected outpatient and oncologist visits, GP and nurse contacts, and use of complete blood counts, biochemistry, computed tomography (CT) scans and chest x-rays. Palliative care costs were also applied.

The submitting company employed a base case diagnostic strategy of upfront testing at diagnosis for EGFR, ALK and ROS1. Only test acquisition costs were considered, based on a claim that NHS Scotland already has the infrastructure in place to perform and analyse both IHC and FISH.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results or the results which do not include the PAS for crizotinib.

Issues relating to the modelled cost-effectiveness analysis include:

- Due to the limited data from the PROFILE 1001 study of patients with ROS1-positive NSCLC, proxy data for ALK-positive patients is employed. Though ROS1-positive and ALK-positive patients may be comparable in terms of their characteristics, there is inherent uncertainty regarding the proxy of ROS1-positive patient outcomes by ALK-positive.
- In both studies there was substantial treatment switching, partially limiting the scope for alternative treatment switching analyses, whilst the RPSFT, the only approach adopted in the model, produced very substantially lower HRs than the unadjusted analyses (potentially reflecting the scale of switching).
- The first line analysis employs covariate adjustment with covariate patterns (baseline characteristics) from North America deemed by the company as more representative of UK clinical practice in place of the patient characteristics seen in the studies. Due to the stratification of analyses in first line there may be some impact on the modelled differences in survival although this is anticipated to be minor.

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

## **Impact beyond direct health benefits and on specialist services**

At the PACE meeting, participants noted that ROS1-positive disease may affect a younger subgroup of NSCLC patients who may still be of working age at diagnosis with dependent families. The response rate achieved and the delayed disease progression would be expected to reduce symptom burden and, with the manageable side effect profile of crizotinib, may allow patients to maintain their quality of life, continue to work and spend more time with their families.

PACE participants also noted that crizotinib is an orally administered treatment, enabling patients to self-administer at home. In contrast to chemotherapy, this would reduce the time spent on hospital visits and the burden of treatment on patients, families and carers. In addition, the more manageable side effect profile may reduce the related impact on services. While, crizotinib may offer advantages over chemotherapy, it was noted that it would not replace the use of chemotherapy. Instead it would offer an additional treatment which may delay the time to chemotherapy. The availability of an effective and well-tolerated additional treatment option also has the potential to reduce the psychological distress associated with this disease.

## Costs to NHS and Personal Social Services

The submitting company estimated there would be 37 patients eligible for treatment with crizotinib in year 1 and 36 patients in year 5. The estimated uptake rate was 100% in year 1 (37 patients) and 100% in year 5 (36 patients).

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.\*

## Conclusion

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

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted crizotinib for use in NHS Scotland.

## Additional information: guidelines and protocols

No guidelines were identified specific to advanced ROS1-positive NSCLC and the guidelines below predate the availability of crizotinib for ROS1-positive NSCLC.

In 2016, the European Society for Medical Oncology (ESMO) published clinical practice guidelines for metastatic NSCLC.<sup>4</sup> The guidelines state that the treatment strategy should take into account the histology, molecular pathology, age, performance status, co-morbidities and patient's preferences. All stage IV NSCLC with a performance status 0 to 2 should be offered systemic therapy. In the first-line treatment of EGFR and ALK-negative disease, it is recommended that platinum-based doublet chemotherapy be used. Cisplatin should be the treatment of choice for those with non-squamous tumours and in patients treated with third-generation regimens, including gemcitabine and taxanes. Pemetrexed is preferred to gemcitabine or docetaxel in patients with non-squamous tumours and should be restricted to non-squamous NSCLC in any line of treatment. Platinum based doublets with a third generation cytotoxic (gemcitabine, vinorelbine or taxanes) are recommended in advanced squamous cell carcinoma patients. The combination of bevacizumab and other platinum-based chemotherapies may be considered in eligible patients with non-squamous NSCLC.\*

The standard of care for patients with EGFR mutations is first-line treatment with an EGFR tyrosine kinase inhibitor (erlotinib, gefitinib or afatinib). Osimertinib is recommended for patients who have developed the EGFR T790M resistance mutation after EGFR tyrosine kinase inhibitors.

Crizotinib is the preferred first-line treatment for patients with NSCLC harbouring an ALK rearrangement and ceritinib is recommended as a second-line agent in patients with progression.

\*It should be noted that due to a non-submission to SMC, bevacizumab is not recommended for the treatment of non-small cell lung cancer within NHS Scotland.

Scottish Intercollegiate Guidelines Network (SIGN) for the management of lung cancer, published in 2014 recommends that in patients with advanced NSCLC who have sensitising EGFR mutation, first line single agent tyrosine kinase inhibitors should be offered.<sup>3</sup> Adding combination systemic anticancer therapy to a tyrosine kinase inhibitor confers no benefit and should not be used. For those patients who have advanced disease, are performance status 0 or 1, have predominantly non-squamous NSCLC and are EGFR mutation negative, 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.

National Institute for Health and Care Excellence guidelines published in 2011 for the diagnosis and management of lung cancer; state that patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100) should be offered chemotherapy to improve survival, disease control and quality of life.<sup>8</sup> For advanced NSCLC this should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. Single-agent chemotherapy with a third-generation drug may be offered to patients who are unable to tolerate a platinum combination.

### Additional information: comparators

Platinum-based doublet chemotherapy, most commonly cisplatin plus pemetrexed.

### Cost of relevant comparators

Medicine	Dose Regimen	Cost per three week cycle (£)
<b>Crizotinib</b>	<b>250mg orally twice daily</b>	<b>3,282</b>
Pemetrexed plus cisplatin, then pemetrexed maintenance	Pemetrexed 500mg/m <sup>2</sup> Cisplatin 75mg/m <sup>2</sup> IV infusion on day one of each cycle Cycles 1 to 4	1,512
	Cycles 5 onwards Pemetrexed 500mg/m <sup>2</sup>	1,440

Doses are for general comparison and do not imply therapeutic equivalence. Costs for crizotinib from eMIMS on 5 February 2018 and based on a three-week cycle for comparison only but crizotinib is given continuously. Costs for pemetrexed and cisplatin from BNF 5 February 2018 are calculated using the full cost of vials/ampoules assuming wastage and are based on a body surface area of 1.8m<sup>2</sup>. Pemetrexed plus cisplatin is usually given for four cycles up to a maximum of six cycles. Costs do not take any patient access schemes into consideration.

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This assessment is based on data submitted by the applicant company up to and including 19 March 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](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 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 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.*