Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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crizotinib, 200mg and 250mg hard capsule (Xalkori®) SMC No. (1152/16)

Pfizer Limited

10 June 2016

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 under the end of life and ultra-orphan process

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

Indication under review: First-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

In patients with previously untreated advanced ALK-positive NSCLC, crizotinib significantly improved progression-free survival compared with a standard systemic anti-cancer therapy.

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

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.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

First-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

Dosing Information

The recommended dose schedule is 250mg twice daily (500mg 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.

If a dose is missed, then it should be taken as soon as the patient remembers unless it is less than six hours until the next dose, in which case the patient should not take the missed dose. Patients should not take two doses at the same time to make up for a missed dose.

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability, refer to the summary of product characteristics for further details.

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

Product availability date

23 November 2015
Crizotinib meets SMC ultra-orphan and end-of-life criteria.

Background

Crizotinib is a selective small-molecule inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase and its oncogenic variants. It is the first targeted therapy licensed for the first-line treatment of ALK-positive NSCLC in the UK.

There are two medicines specifically licensed for use in ALK-positive NSCLC: crizotinib and ceritinib.[1] Crizotinib has previously been accepted for use for the treatment of pre-treated ALK-positive advanced NSCLC by the Scottish Medicines Consortium (SMC). The indication under review is for an extension to the marketing authorisation to use crizotinib as a first-line treatment in advanced ALK-positive NSCLC. Ceritinib is licensed to be used in patients previously treated with crizotinib.[2]

Nature of condition

Advanced ALK-positive NSLCLC is an incurable illness with a high symptom burden and an average survival of around 1 year from diagnosis. ALK-positive NSCLC is a molecularly-defined subgroup of NSCLC patients with an estimated prevalence of 3% to 5%.[1] This sub-type is associated with patients of younger age, adenocarcinoma histology, and a never or light smoking history.[3]

PACE participants reported that patients are often diagnosed when they have advanced disease as they present late with non-specific symptoms. The symptoms related to advanced ALK-positive NSCLC can reduce a patient's ability to carry out activities of daily living with a consequent emotional and physical impact on patients and their families.

In ALK-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 ALK 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.[3,4,5]

In NHS Scotland, regional cancer network guidance recommends that patients with ALK-positive NSCLC receive systemic anti-cancer therapy (SACT) first-line. In 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 currently used in the second-line setting as per its marketing authorisation and the extant SMC advice.[6,7,8] In patients (not selected for ALK status) managed with four cycles of pemetrexed plus platinum and then maintenance pemetrexed, median overall survival from the commencement of induction therapy has been reported as 15.4 and 16.9 months.[9,10] Crizotinib meets SMC ultra-orphan and end-of-life criteria.

Impact of new technology

Summary of evidence on comparative efficacy

The pivotal evidence for this indication is from the multi-centre, open-label, randomised, controlled, phase III study, PROFILE 1014.[11] The study recruited adults (≥18 years) with confirmed locally advanced, recurrent or metastatic non-squamous, ALK-positive NSCLC. Patients were previously untreated for advanced disease, had measurable disease as per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, adequate organ function, and Eastern Co-operative Oncology Group (ECOG) performance status 0 to 2. Patients with brain metastases were eligible if treated and neurologically stable with no ongoing requirements for corticosteroids for at least the previous two weeks.[1,11]

Patients were randomised equally to either crizotinib 250mg twice daily (n=172) or up to six cycles of platinum-pemetrexed SACT (n=171). SACT was given by intravenous (IV) infusion on day one of each 21-day cycle and consisted of pemetrexed 500mg/m^2 plus cisplatin 75mg/m^2 or carboplatin (area under the curve 5 or 6 mg/mL/minute). Choice of platinum agent was at the investigator's discretion. Randomisation was stratified by ECOG performance status (0 or 1 versus 2), race (Asian versus non-Asian) and presence or absence of brain metastases. Treatment was continued until disease progression (as per RECIST), unacceptable toxicity, death or withdrawal of consent. If the investigator considered the patient was gaining clinical benefit, crizotinib could continue beyond disease progression. Patients assigned to SACT could cross over to crizotinib upon disease progression.[11]

The primary outcome was progression-free survival (PFS) which was the time from randomisation to disease progression according to RECIST upon independent radiologic review, or death.[11] At the data cut-off for the primary analysis, 237 events had accrued, 100 in the crizotinib group and 137 in the SACT group.[1] Crizotinib treatment was associated with a statistically significant improvement in PFS compared with SACT, hazard ratio 0.45 (95% confidence interval [CI]: 0.35 to 0.60), p<0.001. The median PFS was 10.9 months and 7.0 months in the crizotinib and SACT groups respectively.[11] Subgroup analyses of PFS consistently favoured crizotinib.[11] No interaction tests were reported to identify any specific between subgroup differences.

At data cut-off, the median duration of follow-up was 17.4 months and 16.7 months in the crizotinib and SACT groups respectively.[11] The study had accrued 44 deaths in the crizotinib group and 46 in the SACT group, an event rate of 26%.[1] Median survival had not yet been reached in either treatment group and the hazard ratio (95% CI) was 0.82 (0.54 to 1.26), p=0.36 (two-sided test). Kaplan-Meier survival probabilities at 12 months were 84% and 79% in the crizotinib and SACT groups respectively.[1,11] Crossover was permitted in the study protocol; at data cut-off, 70% of SACT patients had subsequently received crizotinib treatment. When cross-over was adjusted using the pre-specified rank-preserving structural failure time model with the Wilcoxon test, the hazard ratio (95% CI) was 0.60 (0.27 to 1.42).[11]

In the PROFILE 1014 study, 23% (79/343) patients had brain metastases at baseline. In this subgroup of patients the disease control rate at 12 weeks was 85% (33/39) for crizotinib and 45% (18/40) for patients allocated to SACT, p=0.0003. There was no significant difference between the groups for time to intracranial tumour progression (HR 0.45, p=0.063) but this may be a type 2 error due to the low event rate (27% of patients with baseline brain metastases had progressed).[11]

The objective response rate (best response of either complete or partial responses as per RECIST) associated with crizotinib was significantly greater than in the SACT group, 74% (128/172) versus 45% (77/171), p<0.001. Responses were almost exclusively partial responses; complete responses were recorded in three crizotinib and two SACT patients. Median durations of response (95% CI) were 11.3 months (8.1 to 13.8) in the crizotinib group and 5.3 months (4.1 to 5.8) in the SACT group.[11] Median time to tumour response (time from randomisation to first documented objective response [complete response or partial response]) was 6.1 weeks in the crizotinib group and 12.1 weeks in the SACT group[1].

PROFILE 1014 collected health-related quality of life (HRQoL) data using a variety of tools: the European Organisation for Research and treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30), the lung cancer module (QLQ-LC13), and the EuroQoL (EQ-5D).[12] There was a statistically significant greater improvement in global quality of life measured by EORTC QLQ-C30 for patients treated with crizotinib compared with SACT. The size of the treatment difference (13.8 points) exceeded the minimal clinically important difference of 10 points. Time to deterioration in HRQoL, defined as an increase of at least ten points from baseline in scores for symptoms of chest pain, cough or dyspnoea on EORTC-QLQ-LC13, was significantly longer with crizotinib compared to SACT, median 2.1 versus 0.5 months, with a hazard ratio of 0.59 (95% CI: 0.45 to 0.77), p=0.0005. Most comparisons of the treatments in terms of change from baseline in EORTC QLQ-C30 symptom scores favoured crizotinib (fatigue, pain, dyspnoea, insomnia, and appetite), whereas the comparison of diarrhoea symptom scores favoured SACT. Changes in symptom scores measured with the QLQ-LC13 tool favoured crizotinib with the exception of peripheral neuropathy. General health status scores measured with the EQ-5D visual analogue scale (0 to 100) were significantly improved with crizotinib versus SACT (p<0.05).[1]

Summary of evidence on comparative safety

Almost all patients reported at least one adverse event (AE) during the PROFILE 1014 study. In the crizotinib group, 98% (168/171) had treatment-related AEs compared with 93% (157/169) SACT patients. Treatment-related grade 3 or 4 AEs were reported in 35% and 39% of patients respectively. Treatment-related AEs were associated with permanent discontinuation in 4.7% and 8.3% of crizotinib and SACT patients respectively, dose reduction in 5.3% and 8.3% and temporary discontinuation in 34% and 30% of patients respectively.[1]

In the respective crizotinib and SACT groups, treatment-related grade 3 or 4 AEs included: elevated transaminases (13% versus 2.4%), neutropenia (10% versus 15%), fatigue (2.3% versus 0.6%),

vomiting (1.8% versus 3.0%), leukopenia (1.8% versus 5.3%), pulmonary embolism (1.2% versus 2.4%), anaemia (0 versus 8.3%) and thrombocytopenia (0 versus 6.5%).[1]

Visual disorders of any cause (predominantly grade 1 or 2 in severity) were reported in 71% of crizotinib patients compared with 9.5% of SACT patients.[11]

Grade 5 AEs from any cause occurred in 12% (20/171) of crizotinib patients and in 2.4% (4/169) of SACT patients. With the exception of one case of fatal pneumonitis in a patient who crossed over to crizotinib from SACT, no deaths were considered to be related to crizotinib.[11]

Post-marketing surveillance prompted the Medicines and Healthcare Regulatory Agency to issue advice to healthcare professionals about the risk of cardiac failure associated with crizotinib in November 2015. Patients should be monitored for signs and symptoms of heart failure and dose reduction, interruption or discontinuation considered if heart failure is suspected.[13]

The European Medicines Agency concluded that the safety of crizotinib in ALK-positive NSCLC is consistent regardless of line of therapy (ie when used in first-line or pre-treated patients).[1]

PACE participants highlighted that trial data in the first line setting and experience of use in the second line treatment setting has demonstrated that crizotinib has a better side effect profile than chemotherapy, with less risk of life threatening toxicities. Unlike chemotherapy, crizotinib side effects can often be managed without the need for hospital admission. This advantage allows a treatment option for a wider group of ALK-positive patients where chemotherapy is contra-indicated because of co-morbidities.

Summary of clinical effectiveness issues

The primary outcome measure in the PROFILE 1014 study was PFS, which was assessed by central radiologic review, unaware of treatment allocation, using validated RECIST 1.1 guidelines for tumour assessments. Treatment with crizotinib was associated with a statistically significant improvement in PFS, described as an extension in median PFS from 7.0 to 10.9 months (hazard ratio 0.45).[11] This magnitude of PFS benefit is considered to be clinically meaningful.[1]

The improvement in PFS did not translate into a statistically significant overall survival benefit. However, overall survival data are immature and should be interpreted with caution; 26% of patients in the study had died at the data cut-off. There was substantial crossover of patients from platinum-pemetrexed to crizotinib, confounding the analysis. A number of statistical methods were employed to adjust for crossover. However, given that crizotinib is currently used in patients in NHS Scotland following initial first-line treatment of advanced disease, the hazard ratio (not adjusted for crossover) may well represent the treatment effect expected in NHS Scotland practice.

HRQoL was improved with crizotinib compared with platinum-pemetrexed; treatment-adjusted global health status improvement (measured with EORTC QLQ-C30) exceeded the minimal clinically important difference of 10 points and there was a significant increase in the time to deterioration in quality of life defined by symptoms of chest pain, dyspnoea or cough (measured with EORTC QLQ-LC13). HRQoL assessments may have been biased due to the open-label design of the study.

The choice of platinum agent used was at the investigator's discretion; cisplatin was given to 54% of patients and carboplatin to 46%. The median number of cycles patients received was six.[3] Clinical guidance recommend four cycles of platinum doublet (and treatment should not exceed six).[4,6,7] Pemetrexed maintenance was not specified in the study protocols, and this is a therapeutic option available in Scotland. This may affect the external validity of the study's findings to NHS Scotland practice.

Other factors affecting the external validity of PROFILE 1014 include: the substantial proportion of patients allocated to crizotinib who continued treatment after objective disease progression, and the small proportion of patients (less than 5%) with baseline ECOG performance status of 2. With the recent availability of the ALK-targeted therapy ceritinib, continuation of crizotinib beyond disease progression may not reflect how patients will be treated in practice in the future.

The submitting company stated that a small proportion of patients would receive pemetrexed maintenance therapy or receive a platinum-doublet regimen not including pemetrexed. To support the economic case, the company conducted a Bayesian network meta-analysis (NMA, n=4 studies) of patients with previously untreated advanced NSCLC. Treatments compared were crizotinib, pemetrexed maintenance, and platinum plus gemcitabine, with platinum plus pemetrexed the common comparator in the network. The outcomes compared were overall survival and PFS. The analysis found crizotinib had a high probability of being the best treatment for both outcomes.

There are several weaknesses which limit the internal and external validity of the NMA. Only the crizotinib study recruited patients on the basis of a diagnosis of ALK-positive disease. The submitting company acknowledged that there were substantial clinical differences between the studies which could confound the comparisons and advised caution with interpretation of the NMA results. Examples of clinical heterogeneity include: the number of cycles of the pemetrexed-platinum given, maturity of survival data and the proportion of patients with ALK-positive disease.

Clinical experts consulted by SMC considered crizotinib to be a therapeutic advancement offering the availability of an efficacious targeted therapy in the first-line setting.

PACE participants noted that access to crizotinib as a first line treatment option may also allow patients the opportunity of ceritinib later in the pathway. Ceritinib can only be offered to patients after crizotinib in line with its licence and it provides a further opportunity for an oral treatment option with a favourable adverse effect profile compared to chemotherapy.

As an oral agent which would potentially replace parenteral SACT, the introduction of crizotinib as a first-line treatment option may reduce demand for chemotherapy. However, given the small patient numbers this is unlikely to impact the service substantially.

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

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 crizotinib

The key points expressed by the group were:

- Advanced NSCLC is associated with very poor survival and a high symptom burden that negatively impacts on quality of life for patients, their families and carers.
- Crizotinib may provide a better response rate, extended progression free survival, improved quality of life and reduced intracranial disease progression compared to standard chemotherapy.
- Crizotinib provides a more favourable adverse effect profile over chemotherapy with less risk of serious toxicity and reduced need for hospital admission to manage side effects.

- This oral treatment option offers convenience for patients, their families and carers compared to chemotherapy and consequently will reduce the pressure on NHS services.

- Recognising that patients affected are often younger with dependant families, crizotinib may provide a treatment option that can be offered immediately, with the potential for a quicker, sustained clinical benefit compared to chemotherapy. This may allow patients to maintain activities of daily living, routine working and their overall independence.

- The opportunity to access crizotinib in the first line treatment setting will reassure patients and their families that they are receiving the best standard of care, with the psychological benefit of knowing that alternative options will be available for subsequent lines of therapy when required.

Additional patient and carer involvement
A patient group submission was received from Roy Castle Lung Cancer Foundation. The patient group has received <3% pharmaceutical company funding in the past two years, including from the submitting company. A representative from the patient group participated in the PACE meeting. The keys points of its submission have been included in the full PACE statement.

Value for money

The company presented a cost-utility analysis comparing crizotinib to pemetrexed plus either cisplatin or carboplatin. Comparisons with pemetrexed maintenance and gemcitabine in combination with carboplatin were included as scenario analyses.

A Markov model, with a 30-day cycle, and three health states: progression-free, progressed disease and death was used. All patients began the model in the progression-free state and were at risk of progression and death. Progression was defined in accordance with the PROFILE 1014 study, with progressed disease patients moved to second-line treatment (docetaxel) and then third-line best supportive care (BSC) before death. The model time horizon was 15 years on the basis that this exceeded the life expectancy of most patients. Sensitivity analysis showed changing the horizon to 10 or 20 years made little difference to the results.

Three adjustments were made to the clinical data from the PROFILE 1014 study to:
1. Adjust the results from the study population to be more representative of Scottish patients. These adjustments were based on a North American chart review study (n=147) on the assumption that these patients had similar characteristics to Scottish patients.
2. Adjust for the impact of crossover on the comparator arm data.
3. Continue to treat with crizotinib beyond progression for patients who were still receiving clinical benefit.

PFS and overall survival (OS) curves were fitted in order to extrapolate the data beyond the study period, with the best fit chosen using 3 criteria. For the comparison of crizotinib versus pemetrexed maintenance and crizotinib versus gemcitabine plus carboplatin, PFS and OS were estimated using hazard ratios versus crizotinib, obtained from the NMA.

First-line utility values were taken from the main clinical study which recorded EQ-5D scores. Utility values for patients on docetaxel came from the pivotal study of crizotinib in second-line use, while values for patients assigned to BSC came from a published study. Progression-free disease was valued at 0.81 for patients receiving crizotinib and 0.72 for those assigned pemetrexed plus either cisplatin or carboplatin. Progressed disease was valued at 0.66 whist receiving docetaxel and 0.47 for BSC.

Resource use included medicines costs, administration costs, and the costs of treating adverse events. Costs of ALK testing were included as a sensitivity analysis. Costs were also included for routine care of NSCLC before and after progression.

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount is offered on the list price of crizotinib. With the PAS, the company estimated an incremental cost-effectiveness ratio (ICER) of £48,355 per quality-adjusted life-year (QALY). Comparison of outcomes showed the model predicted that the crizotinib arm increased mean PFS by 4 months (68%) and mean OS by 11.1 months (62%).

In the deterministic sensitivity analysis, the covariates attributed to the OS calculation had the greatest impact on results (ICER varied from £45,516 to £51,270 with PAS). Scenario analyses identified the results were also sensitive to the following:

- Alternative crossover methods resulted in ICERs ranging from £46,742 to £53,370 with PAS.
- Alternative methods to model survival resulted in lower ICERs ranging from £43,839 to £48,147 with PAS.
- Comparing crizotinib to pemetrexed maintenance reduced the ICER with PAS to £38,669.
- Patient characteristics were also an important driver: adopting the study patient population profile reduced the ICER to £42,586 with PAS.

The main strengths of the analysis were the model itself, the clarity of the submission and the range of sensitivity analyses provided. The weaknesses included:

- Immaturity of the OS data, with only 26% of patients having died at the time of data cut, and the substantial crossover of patients from platinum-pemetrexed to crizotinib confounding the analysis.
- Design and conduct of the clinical study had several features which limited its generalisability to the Scottish clinical setting (e.g. small proportion of patients with baseline ECOG performance status of 2, use of docetaxel as second line given availability of ceritinib, continuation of crizotinib beyond disease progression, 6 cycles of pemetrexed plus cisplatin/carboplatin and crossover on progression). The company has considered various methods to address some of these weaknesses but given the key driver for the ICER is OS then each adjustment to OS brings further uncertainty.
- Second-line use in the comparator arm was assumed to be docetaxel not crizotinib. This could not be adjusted for.
- Utility values for PFS in the crizotinib arm appear high, being equivalent to those of the age-matched population in Scotland. A sensitivity analysis using a lower utility value (0.78 compared to 0.81) for PFS in the crizotinib arm indicated the ICER is not particularly sensitive to this parameter. The ICER increased by less than 5% to £50,666.
- Costs to manage rare but serious AEs and any clinician-requested crizotinib-specific monitoring costs were omitted. A sensitivity analysis including a notional cost of £50 a month increased the ICER marginally to £49,474.

Impact beyond direct health benefits and on specialist services

PACE participants highlighted that the ALK positive variant generally affects a younger subpopulation of NSCLC patients who may still be of working age at diagnosis with dependant families that need to be supported financially. The longer duration of response without disease progression, reduced symptom burden and more manageable side effects associated with crizotinib may allow patients to maintain their quality of life and spend more time with their families. This period of stability gives patients, their family and carers more opportunity to come to terms with their terminal condition.

Symptomatic brain metastases are devastating for both patients and their families. Approximately 30% of ALK positive NSCLC may be affected. PACE participants noted that experience with crizotinib has shown that it may increase the time to intracranial disease progression thus markedly improving QoL, avoiding severe disability and hospitalisation. It was also highlighted that palliative radiotherapy can be administered concurrently with crizotinib for patients with bone metastases.

At the PACE meeting it was noted that treatment with this oral formulation enables patients to self-administer at home, freeing up time spent travelling to hospital and receiving chemotherapy treatment, thereby reducing the burden on patients, and their families and carers. Availability of an oral treatment option is potentially associated with a reduction in resource requirements in chemotherapy day units through avoidance of parenteral therapy and associated medical, nursing and pharmacy time. Additionally, unlike chemotherapy, crizotinib side effects can often be managed without the need for hospital admission, reducing the impact on specialist services.

First line crizotinib offers patients and their families a significant psychological advantage over chemotherapy and/or radiotherapy in view of its favourable side effect profile and the opportunity for further lines of treatment if and when the condition progresses on crizotinib. While there is a need for ongoing CT scans and bloods during crizotinib therapy, the frequency of monitoring is less than that required for patients on chemotherapy.

Costs to NHS and Personal Social Services

The submitting company estimated the population eligible for treatment to be 65 in year 1, falling slightly to 61 in year 5, with an estimated uptake of 100% in each year. SMC experts suggest lower patient numbers ranging from 20 to 30 cases per 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.

Conclusion

The Committee 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 the criterion for a substantial improvement in quality of life was satisfied. In addition, as crizotinib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, 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

Scottish Intercollegiate Guidelines Network (SIGN) for the management of lung cancer, published in 2014 recommends that in patients with advanced non-small cell lung cancer (NSCLC) who have sensitising epidermal growth factor receptor (EGFR) mutation, first line single agent tyrosine kinase inhibitors (TKI) should be offered. Adding combination systemic anticancer therapy to a TKI 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.[4]

In 2014, the European Society for Medical Oncology (ESMO) published clinical practice guidelines for metastatic NSCLC.[3] The guidelines state that all stage IV NSCLC with a performance status 0 to 2 should be offered systemic therapy. First line, it is recommended that platinum-based doublet chemotherapy be used. With regards to types of therapy, the guidelines make the following recommendations:

- 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.
- After exclusion of contraindications, bevacizumab combined with a paclitaxel–carboplatin regimen may be offered to patients with non-squamous histology NSCLC and performance status of 0 or 1. The combination of bevacizumab and other platinum-based chemotherapies may be considered in eligible patients with non-squamous NSCLC.*
- Only if platinum therapy is contraindicated should consideration be given to non-platinum-based combination chemotherapy with third-generation agents and should be initiated while the patient has a good performance status. For most patients, four cycles of chemotherapy are recommended, with a maximum of six cycles.
- Patients with NSCLC harbouring an ALK fusion should be offered treatment with crizotinib during the course of their disease

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

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 (World Health Organisation 0, 1 or a Karnofsky score of 80 to 100) should be offered chemotherapy to improve survival, disease control and quality of life. For advanced NSCLC this should be a combination of a single third-generation agent (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 agent may be offered to patients who are unable to tolerate a platinum combination.[9]

All guidelines predate the licensing of crizotinib in the first-line setting.

Additional information: comparators

Platinum-doublet chemotherapy regimens are used first-line in adults with advanced EGFR negative NSCLC. The recommended treatment in patients with non-squamous NSCLC (the subtype in which ALK-positive disease is most commonly indentified) is four cycles of pemetrexed plus platinum with the option to continue with pemetrexed monotherapy as maintenance treatment.

Cost of relevant comparators

Drug	Dose Regimen	Cost per three-week cycle (£)	Cost per course (£)
Crizotinib	**250mg orally twice daily**	**3,282**	**52,517**
Pemetrexed plus cisplatin, then pemetrexed maintenance	IV infusion on day one of each cycle Cycles 1 to 4 Pemetrexed 500mg/m^2 Cisplatin 75mg/m^2 Cycles 5 onwards Pemetrexed 500mg/m^2	Cycles 1 to 4 1,518 Cycles 5 onwards 1,440	23,353
Pemetrexed plus cisplatin	IV infusion on day one of each cycle Cycles 1 to 4 Pemetrexed 500mg/m^2 Cisplatin 75mg/m^2	1,518	6,073

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF on 24 February 2016 and based on body surface area 1.8m^2. The cost per course is based on median of 16 three-week cycles of crizotinib commenced in PROFILE 1014, except for pemetrexed plus cisplatin which is based on four cycles. Costs do not take any patient access schemes into consideration.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 15 April 2016.

*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

Drug 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.