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 end of life process

**nivolumab (Opdivo®)** is accepted for use within NHS Scotland.

**Indication under review**: Treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.

Nivolumab, compared with a standard second-line chemotherapy, significantly increased overall survival in patients with locally advanced or metastatic squamous NSCLC who had received previous therapy including platinum-based doublet chemotherapy.

This advice takes account of 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 nivolumab. 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**

Treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.

**Dosing Information**

3mg/kg by intravenous infusion over 60 minutes every 2 weeks. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Dosing delay or discontinuation may be required based on individual safety and tolerability and further details are provided in the summary of product characteristics.¹

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer. Patients treated with nivolumab must be given the patient alert card and be informed about the risks of nivolumab.¹

**Product availability date**

20 July 2015

Nivolumab within this indication meets SMC end-of-life criteria.

Nivolumab received a positive scientific opinion under the Early Access to Medicines Scheme (EAMS) with the Medicines and Healthcare Products Regulatory Agency for the treatment of advanced lung cancer (characterised by squamous non-small cells) which has spread or cannot be removed by surgery following other cancer chemotherapies on 19 June 2015.

**Summary of evidence on comparative efficacy**

Nivolumab is a human monoclonal antibody that binds to the programmed cell death (PD-1) receptor preventing interaction with PD-1 ligand 1 (PD-L1) and PD-1 ligand 2 (PD-L2), that can be found on tumour cells or other cells in the tumour microenvironment. Binding of these ligands to PD-1 activates negative T-cell regulation, thereby inhibiting T-cell proliferation and cytokine secretion. By blocking this interaction, nivolumab potentiates T-cell responses, including anti-tumour responses. Nivolumab is licensed for the treatment of advanced (unresectable or metastatic) melanoma. The marketing authorisation has been extended to include the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC). It is the first PD-1 inhibitor and immunotherapy medicine to be licensed for treatment of NSCLC and can be used as second-line or later treatment in patients with locally advanced or metastatic squamous NSCLC, which represents approximately 30% of the NSCLC patient population.¹²³

An open-label phase III study (CheckMate 017) recruited 272 adults presenting with locally advanced or metastatic (stage IIIIB or IV) squamous-cell NSCLC with recurrent or progressive disease during or after previous platinum-based doublet chemotherapy. All patients had Eastern Co-operative Oncology Group (ECOG) performance status score of 0 or 1 and measurable disease on computed tomography (CT) or magnetic resonance image (MRI). Randomisation was stratified by prior paclitaxel therapy (yes versus no) and geographic region (United States or Canada versus Europe versus rest of world). Patients were equally assigned to nivolumab 3mg/kg intravenous (IV) infusion every two weeks or docetaxel 75mg/m² IV infusion every three weeks. This was continued until disease progression or discontinuation due to adverse events or other reasons. The primary outcome, overall survival from date of randomisation, was assessed using a log-rank test stratified by prior paclitaxel use and geographic region in the intention-to-treat (ITT) population, which comprised all randomised patients.
Disease progression and objective response were determined by the investigator using the response evaluation in solid tumours (RECIST) version 1.1.\textsuperscript{2,3}

At the first interim analysis, minimum follow-up was 11 months. In the respective nivolumab and docetaxel groups, 64% (86/135) and 83% (113/137) of patients had died. Overall survival was significantly increased with nivolumab compared with docetaxel, with a hazard ratio (HR) of 0.59 (95% confidence interval [CI]: 0.44 to 0.79). In the respective groups, median overall survival was 9.2 months (95% CI: 7.3 to 13.3) versus 6.0 months (95% CI: 5.1 to 7.3) and estimated one-year survival was 42% (95% CI: 34 to 50) versus 24% (95% CI: 17 to 31). In the respective groups, 78% (105/135) and 89% (122/137) had died or had progressive disease. Progression-free survival (PFS) was significantly greater with nivolumab, compared with docetaxel, with a HR of 0.62 (95% CI: 0.47 to 0.81). In the respective groups, median PFS was 3.5 months (95% CI: 2.1 to 4.9) versus 2.8 months (95% CI: 2.1 to 3.5) and estimated one-year PFS was 21% (95% CI: 14 to 28) versus 6.4% (95% CI: 2.9% to 12%). Objective response rate (ORR), defined as a best confirmed objective response of complete response (CR) or partial response (PR), was significantly greater with nivolumab compared to docetaxel, 20% (95% CI: 14 to 28) versus 9% (95% CI: 5 to 15), with an odds ratio of 2.64 (95% CI: 1.27 to 5.49). Median duration of response had not been reached in the nivolumab group and was 8.4 months in the docetaxel group.\textsuperscript{2,4} When the study was stopped early on the basis of this analysis, planned enrolment was complete. Updated analyses, at cut-off in August 2015, when minimum follow-up was 18 months, indicated median overall survival with nivolumab, compared with docetaxel, was 9.2 versus 6.0 months, with a HR of 0.62 (95% CI: 0.48 to 0.81). Estimated survival at 18 months was 28% versus 13%.\textsuperscript{5}

In the nivolumab group, 21% (28/135) of patients continued nivolumab after RECIST-defined disease progression and 32% (9/28) of them met criteria for non-conventional benefit, defined as not having a CR or PR prior to progression, and having one of the following: (1) appearance of a new lesion followed by decrease from baseline of at least 10% in sum of target lesions; (2) initial increase from nadir $\geq$20% in sum of target lesions followed by reduction from baseline of at least 30%; or (3) initial increase from nadir $\geq$20% in sum of target lesions followed by at least two tumour assessments showing no further progression defined as 10% additional increase in sum of target lesions and new lesions.

Quality of life was assessed using the European Quality of Life-5 dimensions questionnaire (EQ-5D), which improved in both groups while on treatment, and the Lung Cancer Symptom scale (LCSS). The LCSS assesses six lung cancer symptoms (appetite, fatigue, cough, dyspnoea, haemoptysis and pain) on 100mm visual analogue scales, with higher scores indicating greater severity of symptoms. The Average Symptom Burden Index (ASBI) is a mean of the six symptom scales and ranges from 0 to 100. Disease-related symptom improvement was defined as a decrease of at least 10 points on ASBI at some point between baseline and week 12. This was achieved by 18% (25/135) and 21% (29/137) of patients in nivolumab and docetaxel groups, respectively. On-treatment mean ASBI generally decreased from baseline with nivolumab, exceeding 10 points after 36 weeks when fewer than 25 patients remained on treatment. It remained stable, with little change from baseline, in the docetaxel group up to week 24 and after this results cannot be interpreted as fewer than 8 patients remained on treatment.\textsuperscript{2,6}

There are supportive data from a phase II study (CheckMate 063) in 117 patients similar to those in the phase III study with disease that had progressed during or after both a platinum-based doublet chemotherapy and at least one other systemic chemotherapy (ie a refractory population). All patients received open-label nivolumab 3mg/kg IV infusion every two weeks. After a median follow-up of 8 months, the primary endpoint, ORR, with nivolumab was 14% (17/177). All 17 patients achieved a partial response. Also 30 patients (26%) had stable disease, with a median duration of 6.0 months. Kaplan-Meier estimated median PFS was 1.87 months (95% CI: 1.77 to 3.15), and median overall survival was 8.21 months (95% CI: 6.05 to 10.91).\textsuperscript{2,7}
Summary of evidence on comparative safety

The adverse event profile of nivolumab has been characterised within the existing indication for use in melanoma and the general safety profile of nivolumab in NSCLC is consistent with this. There were some differences in treatment-related adverse events, with pulmonary events more often reported in NSCLC patients compared to melanoma patients, and skin and endocrine events less frequently reported.²

In the pivotal study (CheckMate 017), 97% of patients in both nivolumab and docetaxel groups reported an adverse event. However, nivolumab was associated with a lower incidence, compared to docetaxel, of grade 3 adverse events, 51% versus 73%; serious adverse events, 47% versus 54%; and adverse events leading to study drug discontinuation, 11% versus 20%. Nivolumab was commonly associated with dyspnoea (37%), cough (31%) and fatigue (30%), and docetaxel was commonly associated with fatigue (40%), neutropenia (33%) and dyspnoea (30%). Within the nivolumab group compared to the docetaxel group, there were lower rates of treatment-related adverse events, 58% versus 86%; with those of grade 3 or 4 severity, 6.8% versus 55%; and those defined as serious, 6.9% versus 24%. The most frequently reported treatment-related adverse events with nivolumab were fatigue (16% [versus 33% for docetaxel]), decreased appetite (11% [versus 19% for docetaxel]) and asthenia (10% [versus 14% for docetaxel]), whereas neutropenia (33%), fatigue (33% [versus 16% for nivolumab]), nausea (23% [versus 9% for nivolumab]), anaemia (22% [versus 2% for nivolumab]) and alopecia (22% [versus 0% for nivolumab]) were the most common with docetaxel. The reduction in frequency of adverse events with nivolumab compared to docetaxel, was mainly, but not completely, due to the large difference in haematological events such as neutropenia and lymphopenia.²³

Adverse events of special interest included immunological adverse events related to nivolumab and were noted as important risks. These included skin, gastrointestinal, pulmonary, endocrine, renal and hepatic events, with the following terms reported in pooled data from the CheckMate 017 and 063 studies: rash (12%), diarrhoea and colitis (9.3%), pneumonitis (5.2%), thyroid disorders (4.4%), nephritis and renal dysfunction (3.2%), hypersensitivity and infusion reactions (1.6%) and liver function abnormalities (1.2%).²

Summary of clinical effectiveness issues

Squamous cell NSCLC presents almost universally in patients with a history of tobacco use and very rarely is it associated with epidermal growth factor receptor (EGFR) activating mutations.² The Scottish Intercollegiate Guidelines Network (SIGN) recommends second-line systemic anticancer therapy with single agent docetaxel or erlotinib for patients with recurrent NSCLC who have been previously treated with first-line systemic anti-cancer therapy for advanced disease.⁸ The erlotinib summary of product characteristics (SPC) notes no survival benefit or other clinically relevant effects of treatment have been demonstrated in patients with EGFR-negative tumours.⁹ Healthcare Improvement Scotland (HIS) has endorsed the National Institute for Health and Care Excellence (NICE) Multiple Technology Assessment (MTA) 374, which recommends that erlotinib should not be used for locally advanced or metastatic NSCLC that test negative for the EGFR mutation.¹⁰¹¹ As the majority of squamous cell NSCLC tumours are EGFR-negative, erlotinib would not be a treatment option for most patients with this disease in Scottish practice. After second-line treatment, various third-line regimens may be used. However, response rates are low and overall survival is very limited, with medians of 4 to 5 months reported.² Nivolumab meets SMC end-of-life criteria.
Clinical experts consulted by SMC considered that there is an unmet need in this therapeutic area, namely for effective therapies, as the prognosis is poor and the symptom burden is high for patients with locally advanced or metastatic squamous NSCLC that is refractory or has progressed following first-line platinum-based doublet chemotherapy. The European Medicines Agency (EMA) also considered that this patient population has a high and urgent unmet medical need. Current treatment choices for these patients are limited.

In the pivotal phase III study, nivolumab, compared with docetaxel, a recognised standard second-line treatment for advanced or metastatic squamous NSCLC, significantly increased overall survival by around 3 months and PFS by around 0.7 months. However, the HR of 0.62 for PFS may be a better indicator of treatment effect. PFS data for medicines that act by stimulating the immune system to destroy tumour cells can be difficult to interpret, as induction of immune and clinical responses may need more time to develop (delayed effect), compared with cytotoxic compounds. Progressive disease may be observed prior to the onset of biological actions or clinical effects. ORR and duration of response were also significantly increased with nivolumab. On-treatment quality of life, as measured by the LCSS, improved with nivolumab from baseline. Also, nivolumab was associated with fewer treatment-related serious and severe adverse events compared with docetaxel, mainly due to a lower incidence of adverse haematological events. Patients receiving nivolumab should be monitored for adverse immune-related events as detailed in the SPC.

The pivotal study excluded patients with ECOG performance status greater than one, thereby limiting application of results to this group of patients. Median age of the study patients was 62 years and about 60% were aged less than 65 years. The study patients were younger than the general NSCLC population, which has median age of 71 years. This may also affect the application of results in practice. Subgroup analyses indicated a different treatment effect in those aged more than 75 years, with a HR for overall survival of 1.85 (95% CI: 0.76 to 4.51). However, as the proportion of the study population aged more than 75 years was small (11%), there is marked uncertainty around this estimate, which may be compounded by an imbalance in ECOG performance status score within this subgroup. Therefore, it is not possible to make robust conclusions on the efficacy of nivolumab in patients aged more than 75 years.

Subgroup analyses appeared to indicate that the treatment effect of nivolumab is not related to tumour PD-L1 status at baseline. Overall survival with nivolumab compared with docetaxel in PD-L1-positive patients (30% [81/272]) had a HR of 0.53 (95% CI: 0.31 to 0.89), and in PD-L1-negative patients (53% [144/272]), the HR was 0.70 (95% CI: 0.47 to 1.02). Although the best responses with nivolumab for overall survival, PFS and ORR were in patients who were PD-L1-positive, responses were observed within PD-L1-negative patients which were comparable or better than those with docetaxel. The EMA noted that role of PD-L1 expression has not been fully characterised and the following factors may have influenced these results: variability within tumours, changes in tumour immune micro-environment with nivolumab treatment, differences in PD-L1 testing on tumour cells versus testing for PD-L1 positivity and PD-L2 status in immune cells, T-cell infiltration and use of archival tissue samples. The expression of PD-L1 and PD-L2 in the tumour micro-environment and the relationship with tumour responses requires further investigation, which is a condition of the marketing authorisation.

In the nivolumab group and docetaxel group, 36% and 30% of patients, respectively, received subsequent systemic anti-cancer treatment, with the most common being chemotherapy, 36% and 24% in the respective groups. In the nivolumab group, 24% received subsequent treatment with docetaxel, and in the docetaxel group, 2% received subsequent immunotherapy. Sensitivity analysis, accounting for differences in subsequent chemotherapy, was consistent with the primary analysis in demonstrating an effect of nivolumab on overall survival (HR of 0.50 (95% CI: 0.35 to 0.71) and, despite the limitations of this type of analysis, were considered supportive of the primary analysis by the EMA.
Patients receiving nivolumab should be continuously monitored for immune-related adverse events up to at least five months after the last dose as an adverse reaction may occur at any time during or after discontinuation of nivolumab therapy.\(^1\)

An indirect comparison of nivolumab with erlotinib was performed and used in an economic sensitivity analysis. However, as noted above, most patients with squamous NSCLC in Scottish practice would not receive erlotinib so the indirect comparison and economic sensitivity analysis were considered to have limited relevance.

Clinical experts consulted by SMC considered that nivolumab for treatment of relapsed or refractory locally advanced or metastatic squamous NSCLC is a therapeutic advancement because of the significantly increased survival and response rates and reduced toxicity compared to the current standard treatment, docetaxel. They considered that the place in therapy of nivolumab would be as a replacement for docetaxel for second-line treatment of locally advanced or metastatic squamous NSCLC.

Clinical experts consulted by SMC considered that the introduction of nivolumab for treatment of relapsed or refractory locally advanced or metastatic squamous NSCLC may impact on the service as it is associated with a more frequent dosing schedule compared to the current standard treatment, docetaxel, that is, IV infusion every two weeks versus every three weeks and with a potentially longer duration of treatment. Docetaxel is typically given for a maximum of four to six doses, whereas there is no maximum duration for nivolumab treatment, with treatment continuing as long as clinical benefit is observed or until it is no longer tolerated by the patient. Nivolumab may be associated with increased monitoring for immune-related adverse events, although it could have fewer adverse events overall and reduced resources associated with these.

### Summary of 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 nivolumab, as an end-of-life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Advanced NSCLC is a devastating incurable disease with marked symptomatology including breathlessness, weight loss, chest pain and fatigue. Squamous NSCLC is a particularly aggressive sub-type of NSCLC.

- Nivolumab represents the first advance in survival in advanced squamous lung cancer since docetaxel was licensed in 1999. Existing second-line options are limited and include docetaxel. Many patients are not fit enough to receive second-line chemotherapy and therefore represent a group with particularly high unmet need.

- Immunotherapy with nivolumab offers a new approach to lung cancer treatment. The median increased survival of 3.2 months compared to second-line docetaxel, was felt to be clinically significant in the context of limited remaining months. Importantly, increased survival is accompanied by improved quality of life as a result of reduced symptoms and improved tolerability of treatment. This is likely to be particularly marked in patients who remain on nivolumab long-term, potentially allowing then to return to a normal level of activity.
• It was noted that the CheckMate 017 study showed a ‘tail of long-term survivors’ with some patients appearing to survive for long periods.

• While delivery of nivolumab requires increased hospital visits and infusions, patients consider this a ‘price worth paying’ for the benefits of treatment. The availability of an additional option following relapse after first-line chemotherapy is very important to patients and provides optimism for the future.

• The PACE group was of the view that this medicine should be made available in NHS Scotland, in line with the licensed indication. Patients who are currently unable to receive second-line chemotherapy and who would otherwise receive supportive care were identified as a group who may derive particular benefit.

**Additional Patient and Carer Involvement**

We received a patient group submission 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.

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**Summary of comparative health economic evidence**

The company submitted a cost-utility analysis which compared nivolumab versus docetaxel in the licensed indication. A partitioned survival model was used to assess the cost-effectiveness of nivolumab versus the comparator using a lifetime time horizon which equated to 20 years. In terms of model structure, the model consisted of three mutually exclusive health states: progression free, progressed disease and death. Patients entered the model in the progression free health state and at the end of each model cycle could remain in that health state or transition to progressed disease or death. Patients who were in the progressed disease health state could also remain in their health state or transition to death. The model assumed that patients were treated with nivolumab or docetaxel in the progression free health state until disease progression.

The sources of the clinical data used in the economic model included the CheckMate 017 study. These data informed estimates of PFS and overall survival (OS) as well as the rate of adverse events. The analysis extrapolated the OS and PFS data from the CheckMate 017 study using parametric functions in order to derive estimates for the economic model. A total of 20 parametric functions were estimated for OS which included standard curves (log-logistic, lognormal and gamma) as well as spline models. Goodness of fit statistics were provided which identified the log-logistic model and the spline 2-knot hazard model as good fits to the observed data. The results of these curves were compared against the study data and real world data to test their validity. The log-logistic curve was identified as the most appropriate curve for the base case analysis in order to model OS.

Utility estimates were derived from the EQ-5D data which were collected as part of the CheckMate 017 study. The analysis also included a disutility for adverse events.

Medicines costs were included in the analysis as well as treatment administration, monitoring, adverse events, disease management and end of life care costs.

A complex Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Group (PASAG) as acceptable for implementation in NHS Scotland.
The base case results indicated that the incremental cost-effectiveness ratio (ICER) for nivolumab versus docetaxel was £46,598 per quality-adjusted life year (QALY). This result was based on an incremental cost of £35,433 and a QALY gain of 0.76. The analysis also estimated a life year gain of 1.31.

The analysis was most sensitive to increasing the OS hazard ratio for nivolumab versus docetaxel to the upper 95% CI value of 0.790 (£82,659) from a base case value of 0.59, using the 2-knot spline hazard function to estimate OS (£56,217), reducing the cost discount rate to 0% (£52,042), increasing the outcome discount rate to 6% (£51,737).

The company also presented a scenario analysis versus erlotinib which generated an ICER of £49,000. This result was based on an incremental cost of £39,776 and an incremental QALY gain of 0.81. A PAS is in place for erlotinib but this analysis used the list price of erlotinib. It is worth noting that the company suggested that this analysis is of limited relevance to the SMC due to the small number of patients expected to receive the medicine in this indication in Scotland. SMC clinical experts also noted that nivolumab is likely to displace docetaxel.

In addition to the comparatively high ICER, the main weaknesses with the analysis were:

- The economic analysis extrapolated the CheckMate 017 data using parametric functions in order to estimate PFS and OS for both nivolumab and docetaxel. However, the SMC Statistical Advisor noted that a large number of curves were presented which appeared a good fit to the study data and a limited number of alternative OS and PFS curves were explored as sensitivity analyses. In addition, the model demonstrated sensitivity to using alternative parametric functions as, when the 2-knot spline hazard function was used to estimate OS, the ICER increased to £56,217. Also, when the 4-knot spline hazard function was used in the economic model for OS, the ICER increased to £54,770 and it is worth noting that this curve was the best fit to the data in terms of goodness of fit statistics for OS. The SMC statistical advisor also noted that it may be inappropriate to validate the survival analysis with registry data as patients in the pivotal study may have poorer outcomes than those in the registries. However, the company response provided additional clarification and data in order to support the similarity of patients in the registries with the pivotal study.
- The analysis assumed that patients were treated until disease progression but a number of patients in the pivotal study were treated with nivolumab beyond progressed disease. As a result, the economic model may underestimate treatment costs if patients remain on nivolumab for longer than the estimated PFS. The company provided a sensitivity analysis where 100% of patients initiated to nivolumab received one dose of the medicine following disease progression which generated an ICER of £48,699. The analysis also assumed that patients would be treated with docetaxel until progression; however, the medicine may only be administered for 4-6 cycles with SMC clinical experts suggesting that 4 cycles was most commonly used. The price applied to docetaxel was also considered high compared to other available costs for the medicine. The company provided a sensitivity analysis where the price of docetaxel was £720 and the number of cycles of docetaxel is limited to 6 which generated an ICER of £50,714.
- The utility values for progression free and progressed disease were high compared to other health technology assessments. The company provided a sensitivity analysis using alternative values in the analysis which increased the ICER to £53,952. In order to explore the combined uncertainty regarding the utility values and the extrapolation of the OS data, a sensitivity analysis was provided which used the alternative utility values in the analysis along with the 2-knot spline hazard model for OS. This analysis generated an ICER of £64,235.

The Committee also considered the benefits of nivolumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that two of the
criteria were satisfied: a substantial improvement in life expectancy in the patient population targeted in the submission and a substantial improvement in quality of life.

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

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

### Additional information: guidelines and protocols

In February 2014 SIGN published guideline number 137, management of lung cancer. This recommends second-line systemic anticancer therapy with single agent docetaxel or erlotinib should be considered for patients with performance status 0-2 recurrent NSCLC who have been previously treated with first-line systemic anticancer therapy for advanced disease.7

In December 2015 NICE issued MTA374: Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy. This recommends that erlotinib is a possible treatment for people with locally advanced or metastatic NSCLC that has already been treated with non-targeted chemotherapy because of delayed confirmation of EGFR-TKI mutation status, if: their cancer tests positive for EGFR-TKI mutation; or, it is not known if the cancer is EGFR-TKI mutation-positive because of problems with the test, and the cancer is very likely to be EGFR-TKI mutation-positive or it responds to the first two cycles of treatment with erlotinib. Erlotinib is not recommended for treating locally advanced or metastatic NSCLC that doesn't test positive for the EGFR-TKI mutation.

On 16 December 2015 HIS issued advice in relation to NICE MTA number 374 (erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy, published in December 2015). It advised that no important differences were identified and the recommendations are as valid for Scotland as for England and Wales.9

Gefitinib is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in people with tumours that are EGFR-TKI mutation-positive. People whose treatment with erlotinib or gefitinib is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.10

### Additional information: comparators

The main comparator is docetaxel monotherapy.

### Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per cycle (£)</th>
<th>Cost per course (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>3mg/kg IV infusion every two weeks</td>
<td>2,414</td>
<td>19,312</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>75mg/m² IV infusion every three weeks</td>
<td>720</td>
<td>2,160</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Doses are based on 70kg body weight and 1.8m² body surface area. Nivolumab and docetaxel costs assume eight and three doses per respective course based on median doses in the CheckMate 017 study. Costs of nivolumab are from the new product assessment form and costs of docetaxel are from BNF online on 12 January 2016. IV = intravenous.
Additional information: budget impact

The company estimated there would be 66 patients eligible for treatment with nivolumab in year 1, increasing to 72 patients in year 5 year, to which confidential estimates of treatment uptake were applied.

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

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


4. Commercial in Confidence*

5. Reckamp K, Spigel DR, Rizvi N, et al. Phase 3, global, randomized trial (CheckMate 017) of nivolumab vs. docetaxel in advanced squamous (SQ) cell non-small cell lung cancer (NSCLC). Presented at the International Association for the Study of Lung Cancer (IASLC) 16th World Conference, Denver US, 6-9th September 2015


9. Roche Ltd. Summary of product characteristics or erlotinib (Tarceva®), last updated 27 January 2014.


This assessment is based on data submitted by the applicant company up to and including 11 March 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.