Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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nivolumab, 10mg/mL, concentrate for solution for infusion (Opdivo®)
SMC No. (1180/16)

Bristol-Myers Squibb Pharmaceutical Limited

09 September 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADCTs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life process

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

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

SMC restriction: treatment with nivolumab is subject to a two-year clinical stopping rule.

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

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.

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

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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

Dosing Information

Nivolumab 3mg/kg administered intravenously (IV) over 60 minutes every 2 weeks.

Treatment with nivolumab should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

Product availability date

May 2016.
Nivolumab received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency as monotherapy for the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adult patients whose tumours express programmed death ligand-1 (PD-L1) on 5 February 2016.

Nivolumab meets SMC end of life criteria for this indication.

Summary of evidence on comparative efficacy

Nivolumab is a human monoclonal antibody that binds to the programmed 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 also licensed for the treatment of squamous NSCLC. The indication under review is the treatment of locally advanced or metastatic non-squamous NSCLC. It is the first PD-1 inhibitor and immunotherapy medicine to be licensed for treatment of NSCLC.[1,2]

CheckMate 057 was a phase III, randomised, international, open-label study in 582 adults with stage IIIB/IV or recurrent non-squamous NSCLC after radiation therapy or surgical resection, and a European Cooperative Oncology Group (ECOG) performance status score 0 or 1. Patients also had disease recurrence or progression during or after one prior platinum-based doublet chemotherapy treatment. If patients had known epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation they were permitted to have received or be receiving an additional line of tyrosine kinase inhibitor therapy. All patients were allowed to have had a continuation of or switch to maintenance therapy with pemetrexed, bevacizumab or erlotinib. Patients with stable central nervous system (CNS) metastases were also included.[3]

Patients were stratified by prior maintenance treatment (yes versus no) and line of therapy (second line versus third line) then randomised equally to receive nivolumab 3mg/kg body weight intravenously (IV) every two weeks or docetaxel 75mg/m^2 body surface area IV every three weeks. Treatment continued until disease progression or unacceptable toxicity. Patients in the nivolumab group could continue treatment beyond initial progression if the investigator considered they were achieving a

clinical benefit and did not have unacceptable side effects. Treatment delay or discontinuation due to adverse events was specified in the protocol. Dose reductions were permitted for docetaxel only.[2,3]

The primary outcome was overall survival measured in all randomised patients. At the interim analysis, after a minimum follow up of 13.2 months, 65% (190/292) and 77% (223/290) of patients had died in the nivolumab and docetaxel groups, respectively. The median overall survival was 12.2 months in the nivolumab group and 9.4 months in the docetaxel group, hazard ratio (HR) 0.73 (95% confidence interval [CI]: 0.59 to 0.89), p=0.002. The overall survival rate at 12 months was 51% and 39%, respectively. After extended follow-up (described as the 18-month analysis, with a minimum follow up of 17.1 months), the median overall survival was still 12.2 months in the nivolumab group and 9.4 months in the docetaxel group, HR 0.72 (95% CI: 0.60 to 0.88), p<0.001. The 18-month overall survival rate was 39% and 23%, respectively.[3]

Two-year overall survival data have recently been presented. In the nivolumab group, 29% (81/292) of patients were still alive at two years compared with 16% (45/290) of patients in the docetaxel group, HR: 0.75 (95% CI: 0.63 to 0.91). Median overall survival was 12.2 months in the nivolumab group and 9.5 months in the docetaxel group.[4]

Tumour response was assessed using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 at week 9 then every six weeks until disease progression. The investigator-assessed confirmed objective response rate (objective response defined as complete or partial response) was 19% in the nivolumab group and 12% in the docetaxel group, p=0.02. The median duration of response was 17.2 months and 5.6 months, respectively.[3]

Median PFS was 2.3 months in the nivolumab group and 4.2 months in the docetaxel group. However, the one-year rate of PFS was 19% in the nivolumab group and 8.1% in the docetaxel group. The HR for disease progression or death was 0.92 (95% CI 0.77 to 1.1), p=0.39.[3] In the nivolumab group, 71 patients (24%) continued treatment after initial progression and 16 had a non-conventional pattern of benefit, i.e. they had a response to treatment after initial disease progression.[2,3]

Of the 582 patients randomised, 78% (n=455) had quantifiable PD-L1 expression. The rates were balanced between the groups (≥1%: 53% and 55%, ≥5%: 41% and 38%, ≥10%: 37% and 35% in the nivolumab and docetaxel groups, respectively). An interaction test suggested a strong predictive association between PD-L1 expression and efficacy of nivolumab at all expression levels, see table 1.[3] No clinically relevant differences in overall survival between nivolumab and docetaxel were found in patients with <1%, <5% and <10% PD-L1 expression.[2]

Table 1. Median overall survival after extended follow up (18-month analysis).[3]

	Median Overall Survival		**Hazard ratio (95% confidence interval)**
	Nivolumab	**Docetaxel**	
≥1% PD-L1 expression level	17.7 months (n=123)	9.0 months (n=123)	0.58 (0.43 to 0.79)
≥5% PD-L1 expression level	19.4 months (n=95)	8.1 months (n=86)	0.43 (0.30 to 0.62)
≥10% PD-L1 expression level	19.9 months (n=86)	8.0 months (n=79)	0.30 (0.27 to 0.58)

Quality of life was measured using the Lung Cancer Symptom Scale (LCSS), this includes six symptom specific questions that address cough, dyspnoea, fatigue, pain, haemoptysis and anorexia. The average symptom burden index is measured on a 0 to 100mm visual analogue scale, with higher scores indicating more symptoms. The minimally clinically important difference is defined as ≥10mm.

The LCSS symptom improvement rate by week 12, defined as the proportion of patients achieving the minimum clinically important difference was 18% (52/292) in the nivolumab group and 20% (57/290) in the docetaxel group. On average, patients in the nivolumab group demonstrated a numerical decrease (improvement) in the LCSS from baseline, whereas those receiving docetaxel showed a numerical increase. Overall, there were no significant changes from baseline measured by the LCSS and quality of life was generally stable on treatment for both groups.[5]

Summary of evidence on comparative safety

The adverse event profile of nivolumab has been characterised within the existing indications and the general safety profile of nivolumab in patients with non-squamous NSCLC was consistent with this.[1,2]

In the pivotal study, 69% (199/287) of patients treated with nivolumab and 88% (236/268) of patients treated with docetaxel reported a treatment related adverse event (TRAE). These TRAE were grade 3 or 4 in 10% and 54% of patients, serious in 7.3% and 20%, and led to study drug discontinuation in 4.9% and 15% in the nivolumab and docetaxel groups, respectively. The difference in grade 3 or 4 adverse events was mainly due to the increased incidence of haematological adverse events in the docetaxel group.[2,3]

Adverse events generally occurred more frequently in patients taking docetaxel. The most common were fatigue (16% versus 29%), nausea (12% versus 26%), decreased appetite (10% versus 16%), asthenia (10% versus 18%), diarrhoea (7.7% versus 23%), peripheral oedema (2.8% versus 10%), myalgia (2.4% versus 11%), anaemia (2.1% versus 20%), alopecia (0.3% versus 25%), neutropenia (0.3% versus 31%), febrile neutropenia (0 versus 10%) and leukopenia (0 versus 10%) in the nivolumab group versus the docetaxel group, respectively.[3]

Adverse events of special interest included immunological adverse events related to nivolumab, these were skin (18%), endocrine (9.4%), gastrointestinal (7.7%), hepatic (5.2%) pulmonary (3.5%), hypersensitivity/infusion reaction (2.8%) and renal events (2.4%).[3]

Summary of clinical effectiveness issues

Locally advanced or metastatic lung cancer is a disease with a high morbidity and mortality. Tobacco use is the most important risk factor for lung cancer, but approximately 10% to 30% of patients with non-squamous NSCLC have never smoked and their disease may be correlated with activating EGFR mutations or other genetic alterations.[2] Estimated overall survival after progression from platinum-based chemotherapy is approximately eight months. Patients with tumours expressing EGFR or ALK mutations may benefit from targeted treatment (erlotinib, afatinib or crizotinib); however, once their disease is resistant to tyrosine kinase inhibitors, patients may experience rapid disease progression.[2] The predominant treatment option after prior chemotherapy is docetaxel, with or without nintedanib in patients with adenocarcinoma. Clinical experts consulted by SMC considered that there is an unmet need in this therapeutic area, as the prognosis is poor and symptom burden is high. Nivolumab meets SMC end of life criteria for this indication.

The primary outcome was overall survival and there was a statistically significant and clinically relevant overall survival benefit associated with nivolumab over docetaxel. Patients receiving nivolumab reported fewer adverse events than patients receiving docetaxel. The symptom improvement rate in the two groups was similar and quality of life from baseline was generally stable for both groups while on treatment. The open-label design could have potentially biased adverse event and quality of life outcomes. A higher proportion of patients in the docetaxel group (7.6%) did not

receive randomised treatment compared to the nivolumab group (1.7%). According to the authors of the published paper, the effect of this on the overall results was minimal.[3] Subsequent systemic anticancer treatment was given to 42% and 50% of patients in the nivolumab and docetaxel groups, respectively. In the nivolumab group, 23% of patients received subsequent docetaxel, and in the docetaxel group, 2% received subsequent immunotherapy.[2]

Patients were enrolled regardless of PD-L1 status and this was not a stratification factor. PD-L1 expression was available for 78% of patients. There was a strong predictive association between PD-L1 expression and efficacy of nivolumab at all expression levels. The European Medicines Agency Scientific Advisory Group for Oncology was convened to discuss the validity of PD-L1 testing and the reliability and usability of PD-L1 as a biomarker in clinical practice. It was considered that PD-L1 expression may be useful to guide decision making but there is not yet enough information to restrict nivolumab use based on PD-L1 expression.[2]

There were a higher number of early deaths (<3 months) in the nivolumab group compared with the docetaxel group (20% versus 15%). Factors associated with early deaths were poorer prognostic factors and/or more aggressive disease combined with low or no tumour PD-L1 expression. The delayed onset of nivolumab effect should be taken into account before initiating treatment in patients with aggressive disease or poorer prognostic features.[1,2]

There were some pre-specified subgroups with HR that numerically favoured docetaxel: third line therapy (n=66, HR 1.34 [0.73 to 2.43]), never smokers (n=118, HR 1.02 [95% CI: 0.64 to 1.61]), EGFR mutation positive (n=82, HR 1.18 [95% CI: 0.69 to 2.00]), rest of the world region (South America, Asia and Australia, n=98, HR 1.49 (95% CI: 0.91 to 2.45]) and patients with CNS metastases (n=68, HR: 1.04 [95% CI: 0.62 to 1.76]). These subgroups were small and the HRs were not statistically significant so no definitive conclusions can be drawn.[2]

Patients with an ECOG performance score ≥2 at baseline, active brain metastases or autoimmune disease, symptomatic interstitial lung disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the clinical study. The summary of product characteristics (SPC) advises that, in the absence of data, nivolumab should be used with caution in these patients after careful consideration of the potential risk-benefit.[1] Few patients aged 75 years and over were included so no conclusion can be drawn on the efficacy of nivolumab in these patients.[2]

The median PFS favoured docetaxel over nivolumab. PFS can be difficult to interpret for medicines that act by stimulating the immune system to destroy tumour cells as induction of immune and clinical responses may need more time to develop (delayed effect) compared to cytotoxic compounds, with progressive disease observed prior to the onset of biological activities or clinical effects. The PFS rate at 1 year favoured nivolumab.[6]

There are no direct comparative data for nivolumab versus docetaxel plus nintedanib or versus best supportive care (BSC). The submitting company presented adjusted indirect treatment comparisons comparing nivolumab with docetaxel plus nintedanib and BSC in patients with non-squamous NSCLC (five studies) and patients with EGFR mutation negative/unknown NSCLC (four studies). The indirect treatment comparisons suggested no significant differences between nivolumab and nintedanib plus docetaxel, measured by overall survival and PFS, and a benefit with nivolumab over BSC in overall survival. The company considered the main weakness of the indirect treatment comparisons was that the proportional hazards assumption did not hold; therefore the results have not been used in the economic case.

Clinical experts consulted by SMC considered that nivolumab for treatment of relapsed or refractory locally advanced or metastatic non-squamous NSCLC is a therapeutic advancement because of the

significantly increased survival and response rates and reduced toxicity compared to a current standard treatment, docetaxel. They considered that the place in therapy of nivolumab would be as a replacement for docetaxel (with or without nintedanib in patients with adenocarcinoma) for second-line treatment of locally advanced or metastatic non-squamous NSCLC.

Clinical experts consulted by SMC considered that the introduction of nivolumab may impact on the service as it has 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. Optimal treatment duration is currently unknown. PD-L1 testing is not routinely available in Scotland at present and there would be also be service implications if the test was introduced to guide selection of patents.

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] Nivolumab may therefore be associated with increased monitoring for immune-related adverse events, although it could have fewer adverse events overall and reduced resource use 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. Patients are often elderly with co-morbities.

- Existing second-line options are limited and include docetaxel with or without nintedanib. 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 within lung cancer and provides a second-line option with considerably less toxicity, favourable survival outcomes and the possibility of sustained response and benefit.

- Importantly it offers potential improvement to quality of life as a result of reduced symptoms and improved tolerability of treatment. Patients who remain on nivolumab long-term may be able return to a normal level of activity and regain independence. Improvement in quality of life is rare in lung cancer and is of major significance to patients and their families.

- 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.

Additional Patient and Carer Involvement

We received patient group submissions from Roy Castle Lung Cancer Foundation (RCLCF), National Lung Cancer Forum for Nurses (NLCFN) and Scottish Lung Cancer Nurses Forum (SLCNF). RCLCF has received <3% pharmaceutical company funding in the past two years, including from the submitting company. NLCFN has received approximately 75% pharmaceutical company funding in the past two years, including from the submitting company. SLCFN has received approximately 80% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from each patient group also participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement.

Summary of comparative health economic evidence

The company presented a cost-utility analysis which compared nivolumab against two comparators; docetaxel, and nintedanib plus docetaxel, in previously treated adult patients with advanced or metastatic non-squamous NSCLC.

A cohort based-partitioned survival model was used to assess the cost-effectiveness of nivolumab versus the comparators using a life 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. The model assumed that patients were initiated on treatment in the progression-free health state, and the duration of time spent in the health state was modelled using time to treatment discontinuation (TTD) as opposed to PFS.

The sources of the clinical data used in the economic model included the CheckMate 057 study, which generated TTD and overall survival (OS) estimates for nivolumab and docetaxel. In addition, the CheckMate 057 study data for nivolumab and docetaxel were extrapolated using the generalised gamma function in order to estimate TTD and OS beyond the pivotal study period. The CheckMate 057 study also provided adverse event data for nivolumab and docetaxel. For the comparison versus nintedanib plus docetaxel, hazard ratios derived from a sub-population of adencarcinoma patients in the LUME-Lung 1 study were applied to the docetaxel arm of the analysis. The OS hazard ratio was applied after 6 months in the model, while the PFS hazard ratio was applied after 2 months. Adverse events data for nintedanib plus docetaxel were taken from the LUME-Lung 1 study.

Utility estimates were derived from EQ-5D data collected as part of the CheckMate 057 study. The analysis also included a disutility for adverse events.

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

A complex 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.

The base case result indicated that the incremental cost-effectiveness ratio (ICER) for nivolumab versus docetaxel was £50,565. This result was based on an incremental cost of £36,830 and a Quality Adjusted Life Year (QALY) gain of 0.73. For the comparison against nintedanib plus docetaxel the ICER was £56,092. This result was based on an incremental cost of £31,046 and a QALY gain of 0.55. A PAS is in place for nintedanib and this was included in the analysis by using an estimate of the relevant price of nintedanib.

The analysis was sensitive to the following changes against each comparator:

Sensitivity Analysis	Versus Comparator (With PAS ICER)	
	Docetaxel	Nintedanib plus docetaxel
Reducing the discount rate for all model costs to 0%	£59,415	£67,291
Increasing the average male body weight to 90kg	£59,333	£67,631
Increasing the discount rate for outcomes to 6%	£56,853	£64,407
Increasing the average body weight for females to 76kg	£54,315	£61,028
Reducing the HR for OS to the lower bound of the 95% confidence interval	-	£72,322

Upon request the company provided subgroup analyses by PD-L1 expression and the results were as follows

- PD-L1 ≥1%: versus docetaxel (£59,381), nintedanib plus docetaxel (£63,726)
- PD-L1 ≥5%: versus docetaxel (£62,176), nintedanib plus docetaxel (£68,616)
- PD-L1 ≥10%: versus docetaxel (£58,032), nintedanib plus docetaxel (£59,249)

Following the New Drugs Committee (NDC) meeting, the company indicated that it wished SMC to consider a base case analysis in which a two-year stopping rule was applied. This resulted in ICERs versus docetaxel and nintedanib plus docetaxel of £27,027 and £25,116 respectively. Additional sensitivity analysis was also provided around the revised base case estimates with the stopping rule applied.

The main weaknesses were:

- There were weaknesses with the modelling of OS and TTD as alternative curves were available which represented a similar fit to the clinical study data and no other curves were tested as sensitivity analyses. In addition, the extrapolation of OS estimated a relatively large gain for nivolumab versus the comparators and it was unclear how plausible the results of the analysis were. For example, mean OS for nivolumab was 13.7 months longer for nivolumab versus docetaxel (26.8 months vs. 13.1 months respectively), which was greater than the estimated total mean survival for docetaxel. The company subsequently provided additional information regarding the extrapolation of OS and a sensitivity analysis which used the 2-knot spline hazard function to estimate OS. This analysis generated ICERs of £34,205 and £34,886 versus docetaxel and nintedanib plus docetaxel respectively for the base case estimate with the stopping rule applied.
- The adjusted indirect comparison which assessed the comparative efficacy of nivolumab versus nintedanib plus docetaxel was associated with limitations and did not report significant differences between nivolumab and nintedanib plus docetaxel in terms of PFS and OS. In addition, the results of this analysis were not used in the economic model, and instead the economic analysis used the results of a second indirect comparison which yielded a significant difference in OS. The SMC Statistical Advisor has commented that the switch to the second indirect comparison was not fully justified and may have represented a naive analysis of the data. In addition, the hazard ratios were calculated through a piecemeal approach which may be subjective and open to interpretation.
- The model structure used TTD data to model PFS although PFS data were available from the pivotal study. If the difference between nivolumab and the comparators in terms of TTD is

larger than the differences in PFS, then by using TTD as a proxy for PFS, the company may have increased the benefit (and utility) for nivolumab. In addition, no significant differences in PFS for nivolumab versus docetaxel were reported in the pivotal study. The company has provided a sensitivity analysis where PFS was used to model progression-free health state occupancy and TTD data were used to model treatment costs. This analysis generated ICERs of £26,904 and £25,059 versus docetaxel and nintedanib plus docetaxel respectively for the base case estimate with the stopping rule applied.

- The base case economic analysis did not include a comparison versus best supportive care (BSC). The New Drugs Committee felt that the patient population who may receive nivolumab in clinical practice could be wider than patients eligible for docetaxel. BSC was therefore identified as a relevant comparator in this indication and a sensitivity analysis comparing nivolumab against BSC was requested from the company. However, the company was not able to provide this analysis because of lack of data.

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 but no modifiers were deemed to apply.

After considering all the available evidence and the output from the PACE process, the Committee was able to accept nivolumab for restricted use in NHS Scotland. Treatment with nivolumab is subject to a two-year stopping rule.

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

Additional information: guidelines and protocols

In February 2014 the Scottish Collegiate Guidelines Network 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.[1]

In December 2015 NICE issued MTA 374: Erlotinib and gefitinib for treating NSCLC 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-tyrosine kinase (TK) mutation status, if: their cancer tests positive for EGFR-TK mutation; or, it is not known if the cancer is EGFR-TK mutation-positive because of problems with the test, and the cancer is very likely to be EGFR-TK 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-TK mutation. 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-TK mutation-positive.[8]

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

Additional information: comparators

Docetaxel, nintedanib plus docetaxel.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per course (£)
Nivolumab	**3mg/kg IV infusion every two weeks**	**2,414**	**14,484**
Docetaxel plus nintedanib	75mg/m^2 IV infusion every three weeks 200mg twice daily on days 2 to 21	2,154	10,771
Docetaxel	75mg/m^2 IV infusion every three weeks	720	2,880

Doses are for general comparison and do not imply therapeutic equivalence. Doses are based on 70kg body weight and 1.8m^2 body surface area. Cost per course assumed six cycles for nivolumab, five cycles for nintedanib plus docetaxel and four cycles for docetaxel. Estimates based on CheckMate 057 study and LUME-Lung 1 study.[3, 7] Costs are from the eMC dictionary of medicines and devices browser on 25 May 2016. IV = intravenous. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The company estimated there would be 200 patients eligible for treatment with nivolumab per year. The uptake rate was estimated to be 11% in year 1 (22 patients), rising to 42% in year 5 (84 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. It should be noted that these templates do not take account of the effects of the two year stopping rule.

*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.

1. Bristol-Myers Squibb. Summary of product characteristics for Opdivo® (nivolumab) in non-squamous NSCLC. 2015.

2. European Medicines Agency. European Public Assessment Report. Nivolumab EMEA/H/C/003985/II/0002. 25 February 2016.

3. Borghaei H, Baz-Ares L, Horn L, Spigel DR, Steins M. Nivolumab versus docetaxel in advanced non-squamous non-small cell lung cancer. N Engl J Med. 2015;373:1627-39.

4. Bristol-Myers Squibb. Press Release: Two-year overall survival data from two pivotal Opdivo® (nivolumab) trials demonstrate sustained benefit in patients with advanced non-small cell lung cancer. BioSpace. 18 May 2016.

5. Horn L, Brahmer J, Reck M, Borghaei H, Spigel DR, Steins M*, et al.* Phase 3, randomized trial (CheckMate057) of nivolumab vs docetaxel in advanced non-squamous (Non-SQ) non-small cell lung cancer (NSCLC): subgroup analyses and patient-reported outcomes (PROs). 18th ECCO 40th ESMO European Cancer Congress

6. European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man, EMA/CHMP/205/95/Rev.4, 13 December 2012.

7. Reck M, Kaiser R, Mellemgaard A, Douillard JY, Orlov S, Krzakowski M*, et al.* Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. The Lancet Oncology. 2014;15:143-55. Epub 01/15.

8. National Institute for Health and Care Excellence (NICE). Multiple technology assessment (MTA) number 374: Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy, December 2015

9. Healthcare Improvement Scotland (HIS). Advice on NICE MTA 374, 16 December 2015 www.healthcareimprovementscotland.org

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