Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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pembrolizumab 50mg powder for concentrate for solution for infusion (Keytruda®) SMC No. (1204/17)

Merck Sharp & Dohme Limited

09 December 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 assessed under the end of life and orphan medicine process

pembrolizumab (Keytruda®) is accepted for restricted use within NHS Scotland.

Indication under review: The treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express programmed death ligand 1 (PD-L1) and who have received at least one prior chemotherapy regimen.

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

Pembrolizumab, compared with a standard taxane monotherapy, significantly improved overall survival in adults with advanced NSCLC tumours that express PD-L1 and have progressed after platinum-doublet chemotherapy.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of pembrolizumab. 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

Published 16 January 2017

Indication

The treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received approved therapy for these mutations prior to receiving pembrolizumab.

Dosing Information

Pembrolizumab 2mg/kg administered intravenously over 30 minutes every three weeks. Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity. Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Patients with NSCLC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test.

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

Patients treated with pembrolizumab must be given the Patient Alert Card and be informed about the risks of pembrolizumab.

Product availability date

29 July 2016

Pembrolizumab received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines Healthcare Products Regulatory Agency on 10 March 2016 for treatment as monotherapy of adults with metastatic NSCLC whose tumours express PD-L1 and whose disease has progressed on or after platinum containing chemotherapy.

Pembrolizumab meets SMC end-of-life and orphan-equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Pembrolizumab is a monoclonal antibody which binds to the programmed death-1 (PD-1) receptor found in T-cells. The PD-1 receptor is a negative regulator of T-cell activity which is involved in the control of T-cell immune responses. PD-L1 and PD-L2 are proteins produced by cancer cells that interact with the PD-1 receptor and switch off the activity of T-cells. Pembrolizumab blocks PD-L1 and PD-L2 from binding to the PD-1 receptor and prevents T-cell deactivation. Pembrolizumab stimulates the body's immune system to target and destroy the tumour.[1]

The key evidence for pembrolizumab in pre-treated advanced non-small-cell lung cancer (NSCLC) is the multi-centre, open-label, randomised, controlled phase II/III study KEYNOTE-010.[2] KEYNOTE-010 recruited adults with NSCLC and measurable disease as per Response Evaluation Criteria in Solid Tumours (RECIST version 1.1). Patients had disease

progression after at least two cycles of platinum-doublet chemotherapy and appropriate tyrosine kinase inhibitors for those with EGFR- or ALK-positive disease. A tumour sample was tested for PD-L1 expression and patients with a tumour proportion score (TPS) ≥1% were eligible. Patients had Eastern Co-operative Oncology Group (ECOG) performance status 0 or 1 and adequate organ function.[2]

Patients were randomised equally to pembrolizumab 2mg/kg (licensed dose, n=345), pembrolizumab 10mg/kg (n=346), or docetaxel 75mg/m^2 (n=343). All treatments were given by intravenous (IV) infusion on day one of a three-week cycle. Treatment was continued for a maximum of 24 months or until disease progression (as per RECIST v1.1) or unacceptable toxicity. Crossover from docetaxel to pembrolizumab was not permitted. Stratification factors for randomisation were ECOG performance status (0 versus 1), region (East Asia or not East Asia); and after allocation of 441 patients, the PD-L1 TPS (1 to 49% versus ≥50%).[2]

There were two primary outcomes in this study, progression-free survival (PFS) and overall survival. PFS was defined as the time from randomisation to radiologically confirmed disease progression or death due to any cause. Disease progression was assessed by independent radiologist using RECIST v1.1. Overall survival was the time from randomisation to death due to any cause. These outcomes were analysed intention-to-treat, which comprised all randomised patients, in the pre-specified sub-group of patients with TPS ≥50% as well as those in the total study population. At the final analysis of outcomes at a data cut-off in September 2015, median follow-up was 13.1 months (for all patients in the study). Results for the licensed dose of pembrolizumab and docetaxel are presented in table 1 below. All outcomes favoured pembrolizumab although PFS in the total study population did not meet the pre-specified threshold for statistical significance.[2]

Table 1: Primary outcomes in KEYNOTE-010

		Pembrolizumab 2mg/kg	Docetaxel
Total study population (tumour proportion score ≥1%)			
PFS	Event rate % (n/N)	77% (266/344)	75% (256/343)
	Median	3.9 months	4.0 months
	Hazard ratio (95% CI)	0.88 (0.74 to 1.05) p=0.07*	
Overall survival	Event rate % (n/N)	50% (172/344)	56% (193/343)
	Median	10.4 months	8.5 months
	Hazard ratio (95% CI)	0.71 (0.58 to 0.88) p=0.0008	
Tumour proportion score ≥50%			
PFS	Event rate % (n/N)	64% (89/139)	78% (118/152)
	Median	5.0 months	4.1 months
	Hazard ratio (95% CI)	0.59 (0.44 to 0.78) p=0.0001	
Overall survival	Event rate % (n/N)	42% (58/139)	57% (86/152)
	Median	14.9 months	8.2 months
	Hazard ratio (95% CI)	0.54 (0.38 to 0.77) p=0.0002	

PFS = progression-free survival. CI = confidence interval
*did not meet pre-specified threshold for statistical significance

A recent analysis at data cut-off March 2016 reported 18-month survival in the total study population of 37% in the pembrolizumab 2mg/kg group and 24% in the docetaxel group. In the sub-group of patients with TPS ≥50%, survival rates were 46% and 24% respectively.[12]

Secondary outcomes were tumour responses (assessed by RECIST v1.1) and duration of response. In the total study population, the objective response rate (ORR), ie the sum of partial and complete responses, was 18% (62/344) in the pembrolizumab 2mg/kg group and 9.3% (32/343) in the docetaxel group, which was statistically significant (p=0.0005, one-sided). The magnitude of the treatment difference was larger in the subgroup of patients with a TPS ≥50%; ORR was 30% (42/139) and 7.9% (12/152), p<0.0001 (one-sided) in the respective treatment groups. In both analysis populations median duration of response had not been reached for pembrolizumab. In docetaxel-treated patients, median duration of response was 6 months in the total population and 8 months in the TPS ≥50% subgroup.[2]

Sub-group analyses showed a significant survival benefit for patients with non-squamous (adenocarcinoma) disease; HR of 0.67 (95% CI: 0.52 to 0.87) for pembrolizumab 2mg/kg versus docetaxel.[3]

The study assessed quality of life using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires C30 and lung cancer specific LC-13 and the EuroQol-5 Dimension (EQ-5D) tool.[2] Analyses concerning the patient-reported outcomes full analysis set (PRO FAS) of the total study population are presented here. The PRO FAS was defined as all randomised patients who took at least one dose of study therapy and had completed at least one PRO assessment.[3] The change from baseline to week 12 in global health status (measured by EORTC QLQ-C30) in all treatment groups were smaller than the minimal clinically important change of 10 points. There was no statistically significant difference between pembrolizumab 2mg/kg and docetaxel for the change in global health status at week 12.[3] Analysis of the data from the EORTC QLQ LC-13 found significant improvements from baseline to week 12 in alopecia, peripheral neuropathy and sore mouth when pembrolizumab 2mg/kg was compared with docetaxel.[4] The time to true deterioration for the composite of cough, chest pain and dyspnoea symptom scores, measured by the EORTC QLQ LC-13, was increased by pembrolizumab compared with docetaxel, although this was not statistically significant.[3, 4] There was no significant difference between the groups for the change in baseline to week 12 in the EQ-5D utility score and for the visual analogue scale.[4]

A small cohort (n=55) of the phase I study KEYNOTE-001 supports the data from KEYNOTE-010. The cohort was treated with the licensed dose of pembrolizumab and had PD-L1 TPS ≥1%, measurable disease, ECOG performance status 0 or 1 and prior treatment with at least one platinum-doublet chemotherapy regimen and relevant tyrosine kinase inhibitor for either EGFR mutation or ALK translocation. At a median follow-up of 7.7 months, the confirmed ORR was 15%, disease control rate (stable, partial and complete response) was 50%, and median PFS was 3.3 months. Median overall survival had not yet been reached, but six-month survival was estimated as 76%.[5]

Summary of evidence on comparative safety

In KEYNOTE-010, the median duration of treatment was 3.5 months in both pembrolizumab groups and 2.0 months in the docetaxel group. Adverse events (AE) related to treatment were reported in 63% (215/339) and 81% (251/309) of pembrolizumab 2mg/kg and docetaxel patients respectively, and grade 3 to 5 events in 13% and 35% respectively. Discontinuation due to treatment-related AE occurred in 4.4% and 10% of patients respectively.

Treatment-related AE of grade ≥3 which may adversely affect a patient's daily living were infrequent. Fatigue was reported in 1.2% and 3.6% of pembrolizumab 2mg/kg and docetaxel patients and diarrhoea in 0.6% and 2.3% of patients respectively. Grade 3 to 5 neutropenia was reported in no pembrolizumab and in 12% of docetaxel patients.

Immune-related adverse events were reported in 20% of patients in the pembrolizumab 2mg/kg group compared with 4.2% of patients in the docetaxel group.[3] The most common events (hypothyroidism, hyperthyroidism and pneumonitis) tended to be grade 1 or 2 in severity. The only grade 3 to 5 immune-related AE which occurred in 1% or more of patients given pembrolizumab 2mg/kg was pneumonitis (2.1%).[2]

Treatment-related deaths occurred in three pembrolizumab 2mg/kg patients (pneumonia and two cases of pneumonitis), and in five docetaxel patients (acute cardiac failure, febrile neutropenia, respiratory tract infection, interstitial lung disease and dehydration).[2]

Summary of clinical effectiveness issues

Pembrolizumab is the second monoclonal antibody for PD-1 to be licensed for NSCLC, after nivolumab. NSCLC accounts for approximately 85% of lung cancers and it is diagnosed at an advanced stage in approximately two-thirds of cases. Systemic anticancer therapy is the standard of care for patients with advanced disease and options include targeted agents against EGFR or ALK (in the presence of disease with EGFR mutation or ALK translocation), or platinum-based chemotherapy. Docetaxel chemotherapy is commonly used after patients have failed platinum-based chemotherapy; however, a proportion of patients are unable to tolerate docetaxel and are managed with best supportive care.[3,6] In practice, a small proportion of patients with adenocarcinoma are currently managed with nintedanib in combination with docetaxel in this setting as per extant SMC advice. Nivolumab is not considered a relevant comparator due to the timing of SMC advice publication for this medicine and indication. In KEYNOTE-010, docetaxel treatment was associated with a median survival of 8.5 months and in patients with adenocarcinoma with unknown PD-L1 expression, median survival associated with nintedanib plus docetaxel was 12.6 months.[2,7] Pembrolizumab meets SMC end-of-life and orphan-equivalent criteria.

The KEYNOTE-010 study provides data for pembrolizumab with the relevant comparator docetaxel. In the total population of patients with PD-L1 expression (TPS ≥1%), pembrolizumab was associated with a statistically significant improvement in overall survival, hazard ratio 0.71. Median overall survival was extended by 1.9 months. There was no statistically significant improvement in PFS in this population of patients. However in the pre-specified subgroup of patients with advanced disease that strongly expressed PD-L1 (TPS ≥50%), there were

clinically significant benefits with pembrolizumab treatment; median overall survival was extended by 6.7 months, and there was a significant improvement in PFS (median extended by 0.9 months).[2] The European Medicines Agency (EMA) noted that although the overall survival results observed in the overall population were clearly driven by the strongly positive PD-L1 sub-group, exploratory analysis in the weakly positive sub-group indicated that the benefit of pembrolizumab was not limited only to the population expressing high levels of PD-L1.[3]

Sub-group analyses showed a significant benefit for patients with non-squamous disease and suggested a clinical benefit for those with squamous disease.[2]

Health-related quality of life was assessed with several validated measures and no significant differences between the treatment groups were reported. [3]

There are a number of factors which may explain failure to demonstrate statistical significance in the co-primary outcome of PFS in the total study population. The study's sample size was powered to detect a significant improvement in overall survival in the sub-group with TPS ≥50%, and the study was assumed to be appropriately powered for the other co-primary outcomes. No formal sample size calculation was conducted for PFS, so the study may not have been sufficiently powered for this analysis.[2] Furthermore, it is accepted that due to the pattern of response associated with these treatments, including the initial appearance of pseudo-progression on radiological imaging, PFS (assessed by RECIST) may not fully capture the clinical benefits associated with immunotherapies.[8]

A high proportion of patients (13%) dropped-out of KEYNOTE-010 prior to receiving the first dose of docetaxel; a consequence of the open-label design of the study.[2] The company considered the risk of bias to be low after comparison of the baseline characteristics of these patients with the whole docetaxel population. While the study protocol did not permit patient crossover to pembrolizumab, 13% of patients assigned to docetaxel subsequently received immunotherapy which may have confounded the analysis of overall survival. The company adjusted for crossover using various techniques.

Patients with active brain metastases were excluded from KEYNOTE-010 although 14% to 16% of patients had stable brain metastases. The study recruited patients who had previous platinum-doublet chemotherapy for their advanced disease.[2] While this is the standard first-line chemotherapy in Scotland;[6] some patients are offered monotherapy with pemetrexed, gemcitabine, or paclitaxel when there is a concern of tolerability with platinum. These factors may limit the generalisability of the results to the Scottish population.

There were no data for the comparison with pembrolizumab and best supportive care which clinical experts indicate may be a relevant comparator.

To support the economic case, the company conducted a Bayesian network meta-analysis (NMA) of pembrolizumab, docetaxel and nintedanib in combination with docetaxel in patients with adenocarcinoma. The network comprised two studies, KEYNOTE-010 and LUME-LUNG-1.[2,7] Outcomes compared were PFS, overall survival, discontinuation due to AEs, and proportion of patients experiencing grade 3 or 4 AEs. The results of the NMA suggest that pembrolizumab may be better tolerated than nintedanib plus docetaxel (odds ratios favouring pembrolizumab) and they may have similar efficacy in terms of overall survival and PFS (hazard ratios close to 1 and credible intervals overlapping 1).

A key assumption of the NMA is that PD-L1 expression status has no impact on the treatment effect of docetaxel or nintedanib plus docetaxel. This may be reasonable given the mechanisms of action of nintedanib and docetaxel. A number of weaknesses and limitations with the data necessitate caution when interpreting the results of the NMA. Comparison of key patient characteristics was not possible for the relevant population of patients with adenocarcinoma. Differences in the maturity of survival data may confound the comparison; in the relevant populations, the event accrual rates for overall survival were 50% and 81% for the pembrolizumab and nintedanib plus docetaxel groups respectively. The comparison of PFS lacks robustness given the non-proportional hazards of docetaxel plus nintedanib versus docetaxel. Furthermore, the different tumour assessment schedule between studies (every nine weeks in the KEYNOTE-010 and every six weeks in LUME LUNG-1) introduces detection bias in the recognition of disease progression. The differences in study design may also confound the comparison of AE profiles: KEYNOTE-010 was open-label and LUME-LUNG-1 was double-blind. In addition, the median duration of follow-up was substantially different between the studies: 13 months and 37 months respectively.

The EMA concluded that there were no new safety concerns with the use of pembrolizumab in patients with NSCLC; however, in comparison with use in patients with melanoma, there appears to be an increased frequency of pneumonitis and respiratory fatalities.[3]

With an increase in the patient groups eligible for pembrolizumab treatment and therefore at risk of immune-related AE, there may be implications for associated services which manage these AE e.g. endocrinology, gastroenterology etc. The eligibility for pembrolizumab relies on the availability of a validated assay to detect PD-L1 expression which is not routinely available in Scotland at present and there will be service implications associated with the introduction of this test. Pembrolizumab provides a second immunotherapy option in this patient group with a poor prognosis. In patients who are not fit enough to take systemic anticancer therapy such as docetaxel, the introduction of PD-L1 inhibitors may provide an alternative treatment option to best supportive care. Clinical experts consulted by SMC noted that pembrolizumab is administered every three weeks, which may be an advantage compared to the alternative PD-1 inhibitor, nivolumab, which is given every two weeks. The optimal treatment duration for PD-L1 inhibitors is currently unknown.

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 pembrolizumab, as an end of life and orphan equivalent medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Advanced NSCLC is a terminal condition with marked symptomatology impacting negatively on quality of life. Symptoms include breathlessness, fatigue, weight loss and chest pain. These symptoms can reduce patients' ability to carry out personal care, cook for themselves or contribute actively to family or business activities.
- Currently the opportunity to access second-line palliative care chemotherapy is limited in view of the frailty and co-morbidity of the affected population. Pembrolizumab may be particularly beneficial for patients with co-morbid conditions that preclude any further chemotherapy e.g. ischaemic heart disease.

- For patients with PD-L1 positive NSCLC and performance status 0 or 1, there is an unmet need that can be served by pembrolizumab and identifying these patients will spare many from the potential for toxicity of chemotherapy while maximising their chance of a durable response.
- Pembrolizumab may offer additional overall survival and a reduced side effect profile leading to improved quality of life for this patient group.
- PACE participants highlighted that any treatment at this stage which is well tolerated is welcomed by family and carers. It may provide time for conversations that help with the psychological impact of bereavement, to enable support services to be put in place including palliative care services, and to address associated practical matters.

Additional Patient and Carer Involvement

We received patient group submissions from Roy Castle Lung Cancer Foundation and Scottish Lung Cancer Nurses Forum, which are both registered charities. Roy Castle Lung Cancer Foundation has received <3% pharmaceutical company funding in the last two years, but none from the submitting company. Scottish Lung Cancer Nurses Forum has received 80% pharmaceutical company funding in the last two years, but none from the submitting company. Representatives from Roy Castle Lung Cancer Foundation and Scottish Lung Cancer Nurses Forum 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 submitted a cost-utility analysis comparing pembrolizumab to docetaxel in patients with PD-L1 positive advanced NSCLC whose disease has progressed on or after prior platinum containing doublet chemotherapy. An economic analysis in a subgroup of these patients with adenocarcinoma tumour histology was also performed, where the comparators were considered to be docetaxel monotherapy, and nintedanib plus docetaxel. The main comparator for the economic analysis in the whole population and sub-group is considered to be docetaxel. Nivolumab is not considered a relevant comparator due to the timing of SMC advice publication for this medicine.

A standard three-state partitioned survival model was used, with health states consisting of progression-free survival, post-progression, and death. A time horizon of 20 years was adopted. For the comparison with docetaxel in the overall PD-L1 patient population, the primary data source for PFS and overall survival (OS) estimation consisted of the phase II/III KEYNOTE-010 comparative study. For the first 52 weeks, the observed OS data from the KEYNOTE-010 study were used for the comparison with docetaxel in the whole PD-L1 patient population and in the adenocarcinoma histology sub-group, with extrapolation beyond this consisting of fitting an exponential function to the remaining data for the docetaxel arm (after adjustment for 13% crossover of docetaxel patients to PD-L1 treatment on disease progression). The same function was applied to phase I KEYNOTE-001 study data for pembrolizumab, which were used on the grounds that the study had longer follow-up than KEYNOTE-010 (this was labelled in the submission as “base case 1”). In an alternative base case (described as “base case 2”), the company provided an analysis in which only the KEYNOTE-010 study data were used for OS extrapolation for both treatment arms. For PFS estimation, the best fitting function (generalised gamma) was fitted to the KEYNOTE-010 data for pembrolizumab and docetaxel from week 9.

To estimate relative effectiveness for nintedanib plus docetaxel in patients with adenocarcinoma histology, hazard ratios for PFS and OS relative to docetaxel alone were derived from the NMA described in the summary of clinical effectiveness issues above. A constant hazard was assumed in the PFS and OS extrapolations for nintedanib plus docetaxel.

Utility estimates were based on analysis of the EQ-5D data derived from KEYNOTE-010 according to time to death, with PFS values of 0.763 if more than 30 days from death and 0.284 if less than 30 days before death, and progressed disease values of 0.675 and 0.320 respectively. Adverse events were derived from the clinical study and utility decrements whilst on treatment were assumed to be captured by the EQ-5D analysis. Costs included were for drug acquisition and administration, PD-L1 testing, adverse event management, subsequent therapies after disease progression, resource utilisation for monitoring and disease management. Treatment with pembrolizumab or docetaxel is until disease progression but in order to take account of discontinuations, duration of treatment was estimated using hazard ratios of time on treatment vs. PFS for pembrolizumab and docetaxel based on KEYNOTE 010 data. It was assumed that pembrolizumab treatment would be discontinued after 2 years in line with the KEYNOTE-010 study protocol. A stopping rule of 6 cycles of docetaxel used either as monotherapy or with nintedanib was applied in line with Scottish clinical practice.

A complex patient access scheme was submitted for pembrolizumab and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The base case 2 analysis represented a relatively standard approach of extrapolation of OS based on the observed phase II/III study data, and is preferred to the use of phase I KEYNOTE-001 study data which has limitations as a basis for OS extrapolation. The with-PAS results of this preferred base case for the overall PD-L1 patient population were estimated at an incremental cost-effectiveness ratio (ICER) of £49,048 per quality adjusted life year (QALY) vs. docetaxel, with an incremental cost of £30,016, incremental life years gained of 0.9, and incremental QALYs of 0.61. For the subgroup with adenocarcinoma histology, the ICER estimated for pembrolizumab (with PAS) vs. docetaxel was £31,657/QALY, based on an incremental cost of £30,220, incremental life years gained of 1.43, and incremental QALYs of 0.96. The ICER estimated for the comparison of pembrolizumab (with PAS) vs. nintedanib plus docetaxel in the adenocarcinoma histology sub-group is £30,534/QALY. A PAS is in place for nintedanib and this was included in the analysis by using an estimate of the relevant price of nintedanib.

Sensitivity analysis demonstrated that the results in the overall patient population and adenocarcinoma subgroup comparisons were most sensitive to uncertainty in the OS estimates extrapolated using the KEYNOTE-001 data, or according to choice of data-cut time point from which to extrapolate OS using KEYNOTE-010 data, dose intensity variation, or varying the HR for time on treatment to PFS for treatment duration estimates. The results were not highly sensitive to applying alternative parametric functions, or alternative approaches to utility assessment, or resource use/cost estimates. Scenario analysis whereby National Lung Cancer Audit Registry data (covering stage IIIB/IV NSCLC patients) were used in order to extrapolate OS beyond 2 years in both treatment arms had a moderate impact on the estimated ICERs.

There were a number of issues with the economic analysis:

- The comparators considered were appropriate, although best supportive care could also be considered an appropriate comparator for the sub-set of patients who are not fit enough to receive further chemotherapy. The company was asked to provide an analysis of

pembrolizumab vs. best supportive care in such patients but stated this was not possible because of the lack of direct or indirect evidence to allow this comparison.

- There are uncertainties in the OS extrapolation vs. docetaxel in the whole PD-L1 population and the adenocarcinoma subgroup associated with the immaturity of the KEYNOTE-010 OS data. For instance, median OS benefit in the KEYNOTE-010 study was estimated at 1.9 months, whereas the projected OS benefit in the model was 0.9 years in the whole population, with most of the life years and QALY gains associated with post-progression survival. In addition, approximately a fifth of the life years gained with pembrolizumab were associated with additional time in the pre-progression state vs. docetaxel despite there being no significant difference in PFS in the KEYNOTE-010 study. However, the company provided additional data which supported the OS extrapolation approach used in the model.
- There was a lack of transparency in the submission regarding the extrapolation of OS in the adenocarcinoma sub-group for the comparison with docetaxel, with a lack of detail on the statistical and visual goodness of fit of parametric functions used in the sub-group analysis. For both the whole patient population and the adenocarcinoma sub-group, the deterministic sensitivity analysis presented in the submission was insufficient to explore the impact of uncertainty in key variables on the pembrolizumab ICERs (including those relating to OS uncertainty, and fitting of parametric functions), and was not provided for the preferred base case 2 analysis.
- The comparison of pembrolizumab vs. nintedanib plus docetaxel in the adenocarcinoma sub-group is limited by concerns with the NMA as described in the summary of the clinical effectiveness issues section above. In addition, the company applied HRs for nintedanib plus docetaxel vs docetaxel rather than use the PFS and OS HRs for pembrolizumab vs. nintedanib plus docetaxel from the NMA, which showed a non-significant difference in OS and would have been more appropriate. As a consequence, the ICERs for the pembrolizumab vs. nintedanib comparison lack robustness and are likely to be underestimated. However, as mentioned above, nintedanib and docetaxel was considered to be a less relevant comparator than docetaxel monotherapy.

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

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

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) issued guidance in 2014 on "Management of lung cancer".[6]

- 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 SACT for advanced disease.
- Second line systemic anticancer therapy with pemetrexed should be considered for patients with advanced non-squamous cell NSCLC who have been previously treated with first line SACT for advanced disease.

The NICE clinical guideline "Lung cancer: diagnosis and management" was published in 2011.[10] Chemotherapy should be offered to patients with stage III of IV NSCLC and good performance status (eg WHO 0, 1 or a Karnofsky score of 80 to 100) to improve survival, disease control and quality of life. Docetaxel as monotherapy should be considered for second-line treatment when appropriate.

"Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines" were published in 2014.[11] Relevant recommendations include:

- Second-line treatment should be offered to patients progressing after first-line therapy; there is no evidence of clinical benefit in using combination regimens in the second line over single-agents.
- Single agents recommended include pemetrexed (for non-squamous histology) and docetaxel. Erlotinib represents a potential second-line treatment option in pre-treated patients with undetermined or wild-type EGFR status.
- Patients with EGFR mutated disease should receive an EGFR tyrosine kinase inhibitor (TKI) if not previously received one.
- Crizotinib is recommended in patients with ALK rearrangement.
- Upon progression after second-line chemotherapy, patients may be candidates for further treatment. Randomised phase III trial evidence is available only for erlotinib, which is indicated for EGFR wild-type patients who have not yet received EGFR TKIs, with performance status 0–3, not eligible for further chemotherapy.

Additional information: comparators

Docetaxel monotherapy, or in those with adenocarcinoma, docetaxel can be given in combination with nintedanib.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)
pembrolizumab	**2mg/kg IV infusion every three weeks**	**3,945**
nivolumab	3mg/kg IV infusion every two weeks	2,414
docetaxel plus nintedanib	Three-week cycle docetaxel: 75mg/m^2 IV infusion (day 1) nintedanib: 200mg orally twice daily (days 2 to 21)	2,154
docetaxel	75mg/m^2 IV infusion every three weeks	720

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from the eMC dictionary of medicines and devices browser on 17 August 2016 and based on 70kg body weight and 1.8m^2 body surface area and includes wastage from unused part-ampoules/vials; costs do not take any patient access schemes into consideration. Cost per course of pembrolizumab 2mg/kg is estimated as £19,725 (median duration of treatment in KEYNOTE-010, 3.5 months ≈ 5 cycles) or £27,615 (mean duration of treatment in KEYNOTE-010, 151 days ≈ 7 cycles).
IV = intravenous.

Additional information: budget impact

The submitting company estimated there would be 183 patients eligible for treatment with pembrolizumab in year 1 rising to 186 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

References

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

1. Merck Sharp & Dohme Limited. Keytruda 50 mg powder for concentrate for solution for infusion - summary of product characteristics. 29 July 2016 [cited 03 August 2016]; Available from: www.medicines.org.uk.
2. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia J L, Han JY*, et al.* Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540-50.
3. European Medicines Agency. Extension of indication variation assessment report: Keytruda (EMA/546566/2016). 23 June 2016 [cited 22 August 2016]; Available from: www.ema.europa.eu.
4. *Commercial in Confidence**
5. Flotten O, Garon E, Arkenau HT, Hui R, Gandhi L, Felip E*, et al.* Pembrolizumab 2mg/Kg Q3W for previously treated, PD-L1 positive advanced NSCLC. Abstract 3024. 16th World Conference of Lung Cancer. September 2015. USA. 2015.
6. Scottish Intercollegiate Guidelines Network. Management of lung cancer. A national clinical guideline (SIGN 137). 2014.
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. Lancet Oncol. 2014;15(2):143-55.
8. European Medicines Agency. Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man: Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials (EMA/CHMP/27994/2008/Rev.1). 01 July 2013 [cited 12 September 2016]; Available from: www.ema.europa.eu.
9. Information Services Division Scotland. Cancer of the trachea, bronchus and lung: ICD-10 C33-34. 2014 [cited 23 August 2016]; Available from: http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Lung-Cancer-and-Mesothelioma/.
10. National Institute for Health and Care Excellence. Lung cancer: diagnosis and management. NICE guidelines [CG121]. 2011 [cited 02 August 2016]; Available from: https://www.nice.org.uk/guidance/cg121
11. Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2014;25(suppl 3):iii27-iii39.
12. Herbst RS, Baas P, Kim D, Felip E, et al. LBA48 Pembrolizumab (pembro) vs docetaxel (doce) for previously treated, PD-L1-expressing NSCLC: updated outcomes of KEYNOTE-010. Presented at ESMO 2016 Congress, Copenhagen 7 to 11 October 2016.

This assessment is based on data submitted by the applicant company up to and including 14 October 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 technologyappraisal: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.