Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Dr Alan G MacDonald

pembrolizumab 50mg powder for concentrate for solution for infusion and 25mg/mL concentrate for solution for infusion (Keytruda®)

SMC No. (1239/17)

Merck, Sharp and Dohme Ltd

09 June 2017

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 equivalent process

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

Indication under review: As monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express programmed death ligand 1 (PD-L1) with a ≥50% tumour proportion score (TPS) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations.

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

In a randomised, open-label, phase III study, treatment with pembrolizumab provided an additional 4.3 months of progression free survival compared to standard of care.

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 the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman,
Scottish Medicines Consortium

Published 10 July 2017

Indication

As monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express programmed death ligand 1 (PD-L1) with a ≥50% tumour proportion score (TPS) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations.[1]

Dosing Information

Pembrolizumab 200mg as an intravenous (IV) infusion 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.

Treatment must be initiated and supervised by specialist physicians experienced in the treatment of cancer.[1]

Product availability date

February 2017
Pembrolizumab meets SMC end of life criteria and orphan-equivalent criteria for the indication under review.

Pembrolizumab received a positive scientific opinion under the Early Access to Medicines Scheme (EAMS) with the Medicines and Healthcare Products Regulatory Agency on 15 March 2016. The indication was as monotherapy of adults with metastatic NSCLC whose tumours express PD-L1 as determined by a validated test and who have not received prior systemic therapy and are negative for EGFR sensitising mutation and ALK translocation.[2]

Summary of evidence on comparative efficacy

Pembrolizumab is a humanised monoclonal antibody which blocks the interaction between the programmed death -1 (PD-1) receptor and its ligands PD-L1 and PD-L2. This results in the functional activity of the target lymphocytes being enhanced to facilitate immune-mediated anti-tumour activity.[1] SMC has previously accepted pembrolizumab for restricted use as monotherapy for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. SMC restricted it to a two-year clinical stopping rule [SMC 1204/17]. The indication currently under review is for first-line use.

The submitting company requested that SMC consider pembrolizumab for first-line use, when administered for a maximum of 35 cycles (i.e. a two year stopping rule). This was the maximum number of cycles used in the pivotal study of pembrolizumab for the indication currently under review.

Evidence of efficacy comes from the pivotal KEYNOTE-024 study, which was of multicentre, randomised, open-label, phase III design. It compared pembrolizumab with the investigator's choice of cytotoxic chemotherapy (standard of care [SOC]) for the first-line treatment of patients with advanced stage IV NSCLC with membranous PD-L1 expression on ≥50% of tumour cells and negative EGFR and ALK status. Patients were aged at least 18 years, had an Eastern Co-operative Oncology Group (ECOG) performance status (PS) of 0 or 1, at least one measurable lesion in accordance with Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 and life expectancy of at least three months.[3]

Patients were randomised equally to pembrolizumab 200mg as a 30 minute IV infusion every three weeks for 35 cycles (n=154) or SOC (n=151), defined as investigator's choice of an IV platinum-based chemotherapy regimen. SOC included four to six cycles of carboplatin plus pemetrexed; cisplatin plus pemetrexed; carboplatin plus gemcitabine; cisplatin plus gemcitabine or carboplatin plus paclitaxel. Patients in the SOC group with non-squamous pathology could receive optional maintenance pemetrexed 500mg/m^2 IV every three weeks. Patients were stratified by ECOG PS (0 versus 1), tumour histological type (squamous versus non-squamous) and region of enrolment (East Asia versus non-East Asia). Treatment was continued for the specified number of cycles or until the patient had radiologic disease progression, treatment-related adverse events (AEs) of unacceptable severity, withdrew consent or until the investigator decided to withdraw the patient, whichever occurred first. However, patients in either group who were clinically stable and were considered by the investigator to be deriving clinical benefit were permitted to continue therapy after disease progression. Furthermore, patients in the SOC group were permitted to cross over to pembrolizumab on disease progression if safety criteria were met.[3]

The primary endpoint was progression free survival (PFS) defined as the time from randomisation to the first documented disease progression (per RECIST v1.1 based on assessment by blinded independent central radiologists' review) or death due to any cause, whichever occurred first. PFS was assessed in the intention to treat (ITT) population. At the second interim analysis (final analysis for PFS) with a median follow-up of 11.2 months, 44% (66/151) of patients in the SOC group had crossed over to pembrolizumab after disease progression and 58% of these patients were still receiving pembrolizumab. After 189 progression events/deaths, median PFS was 10.3 months for pembrolizumab and 6.0 months for SOC; hazard ratio (HR) for disease progression or death 0.50 (95% confidence interval [CI]: 0.37 to 0.68) p<0.001. The estimated proportion of patients who were still alive with no disease progression at six months was 62% in the pembrolizumab group and 50% in the SOC group and at 12 months was 47% and 15%, respectively. Pembrolizumab was statistically or numerically superior to SOC for all pre-specified subgroups including patients with squamous histology.[3, 4]

Secondary endpoints included overall survival and objective response rate (ORR, which included complete plus partial responses assessed using RECIST). At the second interim analysis there were 108 deaths; the estimated proportion of patients who were still alive at six months was 80% in the pembrolizumab group and 72% in the SOC group and at 12 months was 70% and 54%, respectively. Overall survival was significantly longer in the pembrolizumab group compared with SOC; HR for death 0.60 (95% CI: 0.41 to 0.89) p=0.005. Median overall survival was not reached in either group. Due to the beneficial effect of pembrolizumab on survival the study was stopped early after the second interim analysis and all patients in the SOC group were offered pembrolizumab.[3, 4]

ORR occurred in 45% (69/154) of patients in the pembrolizumab group and 28% (42/151) of patients in the SOC group; estimated difference 17% (95% CI: 6% to 27%). The median time to

response was 2.2 months in both groups and the median duration of response was not reached for pembrolizumab and was 6.3 months in the SOC group.[3]

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-LC13 were administered at cycles one to three and then every nine weeks. The least mean change in EORTC QLQ-C30 global health status/quality of life (QoL) score from baseline to week 15 was +6.94 for pembrolizumab and -0.88 for SOC; difference 7.82 (95% CI: 2.85 to 12.79) p=0.002. The proportion of patients with improved global health status/QoL score at week 15 was 40% for pembrolizumab and 26% for SOC. The time to true deterioration endpoint was a composite of EORTC QLQ-LC13 cough, dyspnoea and chest pain questions and was defined as time to first onset of ≥10 point decrease from baseline. The proportion of patients with deterioration events was 30% (46/151) and 39% (58/148) in the pembrolizumab and SOC groups respectively; HR 0.66 (95% CI: 0.44 to 0.97) p=0.029.[4, 5] EQ-5D change from baseline to week 15 in utility and visual analogue scale scores were reported as being consistent with the results observed in analysis of EORTC QLQ-C30.[6]

Supportive data were presented in the company's submission from a cohort of the KEYNOTE-001 phase Ib study. This comprised 101 treatment-naïve patients with histologically or cytologically confirmed stage IV NSCLC, with negative EGFR or ALK status and who had PD-L1 tumour proportion score ≥1%. Patients received unlicensed doses (for first-line treatment) of pembrolizumab; pembrolizumab 2mg/kg every three weeks (n=6), pembrolizumab 10mg/kg every three weeks (n=49) or pembrolizumab 10mg/kg every two weeks (n=46). Data are available with a median follow up of 22.2 months. Twenty-seven patients had a tumour proportion score of ≥50%; in these patients ORR was 52% (14/27), median PFS was 12.5 months, 24-month overall survival rate was 61% and median overall survival was not reached. [7, 8]

Summary of evidence on comparative safety

Treatment-related AEs were reported in 73% (113/154) of patients randomised to pembrolizumab and 90% (135/150) of patients receiving SOC. Grade 3, 4, or 5 treatment-related AEs were reported in 27% (41/154) of patients in the pembrolizumab group and 53% (80/150) of patients in the SOC group and serious treatment-related AEs were observed in 21% (33/154) and 21% (31/150) of patients respectively.[3] Treatment-related AEs led to discontinuation of study treatment in 7.1% (11/154) of patients in the pembrolizumab group and 11% (16/150) of patients in the SOC group.[3]

The most frequently reported treatment-related AEs (with an incidence of ≥10%, any grade) in the pembrolizumab group were diarrhoea 14% (22/154), fatigue 10% (16/154), and pyrexia 10% (16/154). In the SOC group the most frequently reported treatment-related AEs (any grade) were; anaemia 44% (66/150), nausea 43% (65/150), fatigue 29% (43/150), decreased appetite 26% (39/150), neutropenia 23% (34/150), vomiting 20% (30/150), diarrhoea 13% (20/150), neutrophil count decreased 13% (20/150), decreased platelet count 12% (18/150), stomatitis 12% (18/150), constipation 11% (17/150), thrombocytopenia 11% (17/150), decreased white cell count 11% (16/150), dysgeusia 10% (15/150), and blood creatinine increased 10% (15/150).[3]

A total of 29% (45/154) and 4.7% (7/150) of patients in the pembrolizumab and SOC groups respectively had an immune-mediated AE.[3] Immune-related grade 3 or 4 AEs were observed in 10% (15/154) and <1% (1/150) of patients in the pembrolizumab and SOC groups respectively. Immune-mediated grade 3 or 4 AEs (occurring in two or more patients) were only reported in the

pembrolizumab group; severe skin reaction 3.9% (6/154), pneumonitis 2.6% (4/154), and colitis 1.3% (2/154).[3]

Summary of clinical effectiveness issues

Around two-thirds of patients with NSCLC are diagnosed at an advanced stage. NSCLC can be subdivided into non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types) and squamous cell (epidermoid) carcinoma.[4] The proportion of people with advanced NSCLC with membranous PD-L1 expression on ≥50% of tumour cells is approximately 23% to 28%.[3] Patients with advanced NSCLC who are EGFR mutation negative are currently treated in the first-line setting with four cycles of cisplatin plus pemetrexed (non-squamous) followed by maintenance pemetrexed or, in patients with squamous pathology, cisplatin/carboplatin and a third generation agent (docetaxel, gemcitabine, paclitaxel or vinorelbine).[9] Pembrolizumab meets SMC end of life and orphan-equivalent criteria. Pembrolizumab was available under the EAMS as monotherapy for adults with metastatic NSCLC whose tumours express PD-L1 as determined by a validated test and who have not received prior systemic therapy and are negative for EGFR sensitising mutation and ALK translocation.[2] The submitting company requested that SMC consider pembrolizumab when administered for a maximum of 35 cycles, the maximum number of cycles used in the pivotal study of pembrolizumab.

In the pivotal study, KEYNOTE-024, the median number of cycles in the pembrolizumab and SOC groups was 10.5 and 4, respectively. Treatment with pembrolizumab provided an additional 4.3 months of PFS compared to SOC and PFS was superior in all subgroups including patients with squamous histology, where there are limited effective treatments. Pembrolizumab was also significantly better than SOC for overall survival, although medians have not been reached in either group. The study was stopped, after the second interim analysis, due to the significant benefits observed in survival despite confounding due to crossover. Long term data are very limited with a median follow-up of 11.2 months.[3] Results from an overall survival analysis based on 170 death events will be available in June 2018, but will be limited by cross over.[4]

Cross over was permitted for patients treated with SOC who progressed; 44% (66/150) of patients crossed over and 58% of these patients were still receiving pembrolizumab at the data cut off for the second interim analysis.[3] The rank preserving structural failure time (RPSFT) was the pre-specified analysis for dealing with cross over in the study's statistical plan.[4]

Patients in either group who were in a clinically stable condition and were considered by the investigator to be deriving clinical benefit could continue therapy after disease progression.[3] While the summary of product characteristics (SPC) notes that patients should be treated until disease progression (or unacceptable toxicity) it also recommends to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.[1]

In the study 44% (67/151) of patients in the SOC group received cisplatin plus pemetrexed and 30% (46/151) received pemetrexed maintenance.[3] Use of platinum containing doublet regimens in the SOC group concords with recommended guidance in NHS Scotland.[3, 9] In practice a small number of patients who are unfit for platinum chemotherapy may receive single agent chemotherapy and results of KEYNOTE-024 may not be generalisable to these patients. However, the implications of this are negligible given the small number of patients that this will affect.

Patient reported outcome data are limited to analysis at 15 week time points and therefore the effect of pembrolizumab on patient reported outcomes beyond this time point is currently unknown.[4]

The supportive phase Ib study, KEYNOTE-001, which recruited 27 patients with treatment naïve stage IV NSCLC and PD-L1 tumour proportion score ≥50%, has limited applicability given that patients were not treated with the first-line licensed dose of pembrolizumab.[7, 8]

All patients with advanced NSCLC with no EGFR or ALK positive tumour mutations will require PD-L1 testing to obtain the tumour proportion score in order to ascertain eligibility for pembrolizumab. PD-L1 testing is now available at three laboratories in NHS Scotland. Treatment with pembrolizumab will require IV infusions every three weeks for up to 35 cycles which will have service and patient implications compared with current Scottish clinical practice for patients with squamous NSCLC where four cycles of platinum containing doublet chemotherapy are given. Although patients with non-squamous NSCLC may currently receive maintenance therapy with pemetrexed every three weeks following four cycles of doublet chemotherapy.

Pembrolizumab will offer an alternative first-line treatment for patients which may be better tolerated than current chemotherapy regimens. This was also noted by clinical experts consulted by SMC who considered pembrolizumab was a therapeutic advancement. The safety profile of pembrolizumab observed in KEYNOTE-024 was consistent with that seen previously with pembrolizumab for the treatment of advanced NSCLC and other tumour types. Most immune-mediated events were grade 1 or 2, and none led to death.[3] The SPC notes that immune-related AEs that occurred in patients on treatment were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. It also notes that immune-related AEs may occur after the last dose of pembrolizumab.[1]

A fixed dose of pembrolizumab (200mg IV every three weeks) was used in KEYNOTE-024 and was based on modelling and simulations which showed consistent exposure compared to pembrolizumab 2mg/kg. This dose is licensed for first-line treatment of advanced NSCLC and differs from the pembrolizumab dose licensed in the second-line setting (2mg/kg IV every three weeks).[1, 3, 4]

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

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of 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 devastating, incurable cancer which results in significant symptom burden for patients and their families/carers. These include physical symptoms such as loss of energy, breathlessness, pain and sleeplessness and psychological and emotional symptoms such as anxiety and depression.

- Chemotherapy regimens currently used first-line may be associated with poorer outcomes and significant adverse events that are often not tolerated. Adverse events include lethargy, fatigue, bone marrow depression, mucositis and peripheral neuropathy. The availability of pembrolizumab will address unmet need particularly for those patients unsuitable for chemotherapy regimens.

- Pembrolizumab may provide an additional four months of progression free survival compared to chemotherapy, with the potential for accompanying improvements in quality of life. It would appear that overall survival may also be prolonged.

- The additional time that pembrolizumab offers allows families greater opportunity to come to terms with the patients illness and decline. Families/carers will also benefit from the improved quality of life that patients will experience.

Additional Patient and Carer Involvement

We received patient group submissions from the Roy Castle Lung Cancer Foundation and the Scottish Lung Cancer Nurses Forum. The Roy Castle Lung Cancer Foundation is a registered charity and the Scottish Lung Cancer Nurses Forum is an unincorporated organisation. The Roy Castle Lung Cancer Foundation has received 6.1% pharmaceutical company funding in the past two years, with none from the submitting company. The Scottish Lung Cancer Nurses Forum has received 80% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing pembrolizumab to SOC in adults with metastatic NSCLC whose tumours express PD-L1 with a ≥50% tumour proportion score, with no EGFR or ALK positive mutations, and are previously untreated with systemic chemotherapy. The submitting company requested that SMC consider pembrolizumab for first-line use, when administered for a maximum of 35 cycles (i.e. a two year stopping rule). SOC refers to platinum-based doublet chemotherapy options with/without pemetrexed maintenance therapy. Due to a lack of evidence and small numbers of patients expected, an economic case has not been made for patients unable to tolerate platinum based chemotherapy.

A standard three-state partitioned survival model was used, with health states consisting of PFS, post-progression, and death. A time horizon of 20 years was adopted. For the comparison with SOC the primary data source for PFS and overall survival estimation was the phase III KEYNOTE-024 comparative study.[3] A two-phase piecewise modelling approach was taken. For the first 22 weeks the observed overall survival data from the KEYNOTE-024 study were used for the comparison with SOC with extrapolation beyond this consisting of fitting an exponential function to the remaining data for SOC (after adjustment for crossover of patients from SOC to pembrolizumab using a two-stage correction approach). For PFS estimation, the best fitting function (Weibull) was fitted to the KEYNOTE-024 data for pembrolizumab and SOC from week 9.

Utility estimates were based on pooled analysis of the EQ-5D data derived from KEYNOTE-024 according to time to death, regardless of whether the patient had progressed or not, with a value of 0.808 if more than 360 days from death, 0.712 if 180-359 days from death, 0.598 for patients

30-179 days from death, and 0.48 if less than 30 days before death. These were age- adjusted in the base case. AE rates were derived from the clinical study and utility decrements whilst on treatment were determined by comparing progression-free survival EQ-5D data from the study for those patients who had grade 3-5 AEs to those who did not.

Costs for drug acquisition, administration, subsequent therapies, AEs, PD-L1 testing, and health-state costs (e.g. monitoring, disease management, terminal care relating to progression-free and post-progression patients) were all included in the economic analysis. Time on treatment was estimated by fitting parametric functions to the observed clinical study data for time to treatment discontinuation for each treatment arm (Weibull for pembrolizumab, and generalised gamma for SOC). Treatment with pembrolizumab or SOC is continued until disease progression but it was assumed that pembrolizumab treatment would be discontinued after a maximum of two years (35 cycles) in line with the KEYNOTE-024 study protocol. A stopping rule of 18 weeks (six cycles) for the SOC chemotherapies was applied in line with Scottish clinical practice and the KEYNOTE-024 protocol. Subsequent second-line treatment was assumed to consist of eight cycles of docetaxel in both treatment arms based on that received in the KEYNOTE-024 study.

A patient access scheme (PAS) has been submitted for pembrolizumab and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The corresponding base case incremental cost per quality adjusted life year (QALY) gained with the PAS discount is £41,213/QALY, based on an incremental cost of £49,739, an incremental life year gain of 1.53 and a QALY gain of 1.21 (Table 1). Almost all of the overall survival benefit is associated with longer time estimated in the pre-progression state with pembrolizumab.

Table 1: Results for pembrolizumab vs. Standard of Care

Analysis	ICER with PAS price of pembrolizumab
Base case	£41,213
No crossover adjustment of overall survival (note costs of pembrolizumab in patients who crossed over was not included in this analysis)	£48,971
Crossover adjustment using the RPSFT method	£38,871
Crossover adjustment using the IPCW method	£40,807
SOC PFS extrapolation based on exponential (best statistical fit) rather than Weibull	£41,182
Chemotherapy drugs in SOC based on market share data for Scotland	£40,848
EQ 5D derived Utilities for progression free (0.778) and disease progression (0.668) applied	£42,874
10% lower utilities based on time to death analysis	£45,895
Assuming 5% OS at 5 years for SOC (based on NLCA data)	£49,053
Applying 30 week time point for extrapolation of OS data	£50,512
Applying a 3 year stopping rule for pembrolizumab (52 cycles maximum)	£51,925
No stopping rule for pembrolizumab or SOC (i.e. duration based on time on treatment extrapolation	£84,868

One way sensitivity analysis demonstrated the base case ICER for pembrolizumab vs. SOC appeared most sensitive to the extrapolation of overall survival (for both treatment arms, but especially for pembrolizumab), and utility values for longer term survivors (i.e. >360 days) (see Table 1).

Scenario analyses considering applying different methods of adjusting for crossover, alternative extrapolation approaches for PFS, using Scottish market share estimates for the comparator drugs, and alternative utility estimation methods, had a relatively small impact on the ICER (Table 1).

There were a number of key issues with the economic analysis:

- The overall survival data used as a base for the economic model are immature, and cross-over of 44% of patients from SOC to pembrolizumab contributes to confounding of the relative survival estimates. Advice from the SMC statistician was that the statistical adjustment was performed appropriately, and the ICER did not vary significantly with type of cross-over adjustment method adopted (see Table 1).
- There is some uncertainty with the overall survival estimates for SOC relative to that expected in clinical practice – the model predicts a 1.9% survival rate at five years for SOC after cross-over adjustment whereas an analysis of data from the National Lung Cancer Audit (NLCA) Registry has estimated a 5% overall survival at 5 years for current SOC in stage IV performance status 0-1 patients.[10] Scenario analysis was requested from the company using the NCLA- derived estimate of overall survival and resulted in an ICER of £49,053/QALY with PAS (Table 1). The company in response argued a 5% overall survival for SOC was likely to be an overestimate as the NLCA data contained patients with relatively good prognosis, and provided an analysis of data extracted from the Cancer Analysis System in patients with stage IV NSCLC which showed a 5 year overall survival of 1.5% for the years 2007-11.[11]
- Whilst the time to death approach to utility estimation is useful to account for health related quality of life decline with disease progression, estimates are based on quite small patient numbers, especially for the 180-360 days, and <30 days before death states (n=26 and 21 respectively). Also, the utilities across these states and those for the alternative scenario using conventional pre-progression and post progression states seem high relative to population norms and previous cancer HTAs. A scenario analysis was requested assuming 10% lower utility across health states, which resulted in ICERs with PAS of £45,895/QALY for the base case time to death based analysis (Table 1) and £42,874/QALY using progression based utility approach.
- Duration of treatment with pembrolizumab in the economic model has been capped at two years. This is in line with the KEYNOTE-024 study protocol. Whilst this may be reasonable to assume in the base case given the trial protocol and clinical evidence presented, the impact of relaxing the stopping rule assumption on the ICER was not explored in the company submission. Hence further scenario analysis was requested assuming a stopping rule of 3 years, which increased the ICER to £51,925/QALY with PAS, and using the extrapolated time on treatment estimates for both pembrolizumab and SOC comparator (ie assumes no stopping rules applied) resulted in an ICER estimate of £84,868/QALY with PAS.

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

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

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

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network published guideline number 137, Management of lung cancer in 2014. Patients who have advanced disease, are performance status 0 to 1, have predominantly non-squamous NSCLC and are EGFR mutation negative should be offered combination systemic anticancer therapy with cisplatin and pemetrexed. All other patients with NSCLC should be offered combination systemic anticancer therapy with cisplatin/carboplatin and a third generation agent (docetaxel, gemcitabine, paclitaxel or vinorelbine). Platinum doublet systemic anticancer therapy should be given in four cycles; it is not recommended that treatment extends beyond six cycles. First line single agent tyrosine kinase inhibitors should be offered to patients with advanced NSCLC who have a sensitising EGFR mutation.[9]

The European Society for Medical Oncology (ESMO) published metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, in 2016. Patients with EGFR- and ALK-negative stage IV non-squamous or squamous cell carcinoma without major comorbidities and PS 0 to 2 should receive cisplatin or carboplatin plus a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) in first-line setting. In addition, patients with non-squamous cell carcinoma may receive a pemetrexed containing doublet regimen (and pemetrexed maintenance) in first-line setting.[12]

These guidelines predate the availability of pembrolizumab for first-line treatment of advanced NSCLC.

Additional information: comparators

Non-squamous histology: cisplatin plus pemetrexed, followed by maintenance pemetrexed
Squamous histology: cisplatin/carboplatin plus docetaxel, gemcitabine, paclitaxel or vinorelbine.

Cost of relevant comparators

Medicine	Dose regimen	Cost per cycle (£)
Pembrolizumab	**200mg IV infusion on day 1 every 3 weeks**	**5,260**
Pemetrexed* Cisplatin≠	500mg/m^2 IV infusion on day 1 75mg/m^2 IV infusion on day 1 every 3 weeks	1,414
Gemcitabine Cisplatin≠	1,250mg/m^2 IV infusion day 1 and 8 75mg/m^2 IV infusion day 1 every 3 weeks	153
Vinorelbine Cisplatin≠	60 to 80mg/m^2 orally day 1 and 8 75mg/m^2 IV infusion on day 1 every 3 weeks	558 to 690

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis, DM&D and MIMs on 1 March 2017. Costs do not take any patient access schemes into consideration.A body surface area of 1.8m^2 was used for dose calculations, when applicable. Costs for additional vitamin supplements and corticosteroids for pemetrexed have not been included. *Following four cycles of pemetrexed plus cisplatin, pemetrexed may be given as maintenance therapy on day one of a three-week cycle (cost per cycle=£1,340). ≠Cisplatin may be replaced by carboplatin in patients with poor renal function (e.g. pembrolizumab 400mg [based on glomerular filtration rate 55mL/min and area under curve 5mg/mL/min regimen]: cost of carboplatin per cycle=£140). Regimens are for illustrative purposes only; not all regimens have been included. IV= intravenous.

Additional information: budget impact

The submitting company estimated there would be 156 patients eligible for treatment with pembrolizumab in year 1 rising to 159 patients in year 5 to which confidential estimates of treatment uptake were applied. The budget impact estimate included the additional costs of PD-L1 testing.

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

1. Merck Sharp and Dohme Ltd. Summary of product characteristics for pembrolizumab (Keytruda). Last updated 2 February 2017.
2. Medicines, Healthcare Products Regulatory A. Pembrolizumab NSCLC Early Access to Medicines Scientific Opinion - Public Assessment Report. 2016.
3. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A*, et al.* Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016.
4. European Medicines Agency. Extension of indication variation assessment report. Pembrolizumab Procedure No. EMEA/H/C/003820/II/0011.
5. Brahmer J, Rodriguez-Abreu D, Robinson A et al. PL04a: Immune checkpoint inhibitors in advanced NSCLC (ID430). International Assocation for the Study of Lung Cancer. 2016; .
6. *Commercial In Confidence**
7. Hui R, Gandi L, Carcereny E, et al. Long-Term Overall Survival For Patients With Advanced NSCLC Enrolled In the KEYNOTE-001 Study of Pembrolizumab. J Clin Oncol. 2016;34((15 Supp):9026. abstract).
8. Hui R, Garon EB, Goldman JW, et al. Pembrolizumab as first-line therapy for patients with PD-L1–positive advanced non–small cell lung cancer: a phase 1 trial. Annals of Oncology. 2016;Pending publication.
9. Scottish Intercollegiate Guidelines Network. SIGN 137: Management of lung cancer. 2014 [cited.
10. British Thoracic Society. Sharing Information with Lung Cancer Patients: Guidance for Healthcare Professionals Discussing Options for Patients who have Lung Cancer. British Thoracic Society reports. 2013;5(1).
11. Cancer Analysis System (Public Health England). 2017.
12. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG*, et al.* Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v1-v27.

This assessment is based on data submitted by the applicant company up to and including 17 April 2017.

**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

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a 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.