Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2207

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

Merck Sharp & Dohme Ltd

06 September 2019

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 NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission assessed under the end of life process

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

Indication under review: in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma (NSCLC) in adults whose tumours have no EGFR or ALK positive mutations.

SMC restriction: in patients whose tumours express programmed death ligand 1 (PD-L1) with a <50% tumour proportion score (TPS), or in those whom it has not been possible to evaluate PD-L1 TPS. Treatment with pembrolizumab is subject to a two-year clinical stopping rule.

The addition of pembrolizumab to pemetrexed and platinum chemotherapy significantly improved progression-free survival and overall survival in patients with metastatic non-squamous NSCLC with no EGFR or ALK mutations.

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 NHSScotland 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 07 October 2019

Indication

In combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma (NSCLC) in adults whose tumours have no Epidermal Growth Factor Receptor (EGFR) or Anaplastic Lymphoma Kinase (ALK) positive mutations.[1, 2]

Dosing Information

Pembrolizumab as part of combination therapy should be administered at a dose of 200mg via intravenous infusion over 30 minutes every 3 weeks.

Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity. Atypical responses (that is 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.

Testing for PD-L1 tumour expression using a validated test is recommended for patients with NSCLC. In patients with non-squamous NSCLC whose tumours have high PD-L1 expression, the risk of adverse reactions with combination therapy relative to pembrolizumab monotherapy should be considered and the benefit/risk ratio of the combined therapy evaluated on an individual basis.

See the summary of product characteristics (SPC) for further information regarding advice for treatment modification for adverse events.[1, 2]

Product availability date

September 2018
Pembrolizumab meets SMC end of life criteria for this indication.

Summary of evidence on comparative efficacy

Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor found in T-cells and blocks its interaction with ligands PD-L1 and PD-L2, resulting in immune-mediated anti-tumour activity.[1, 2] SMC has previously accepted pembrolizumab for restricted use in metastatic non-small cell lung carcinoma (NSCLC) in the following settings, both subject to a two-year stopping rule:

- as monotherapy for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% tumour proportion score (TPS) and who have received at least one prior chemotherapy regimen [SMC 1204/17]

- as monotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥50% TPS with no EGFR or ALK positive tumour mutations [SMC 1239/17]

This resubmission is for use of pembrolizumab in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations. In the resubmission, the company has focussed on the patient population with PD-L1 TPS<50%, since current treatment options are limited for patients with PD-L1 TPS <50%, and pembrolizumab monotherapy has been accepted by SMC for patients with PD-L1 TPS ≥50%. The submitting company also requested that SMC considered positioning pembrolizumab for use in those whom it has not been possible to evaluate PD-L1 TPS.

The key evidence of efficacy comes from the KEYNOTE-189 study; an ongoing, randomised, double-blind, phase III study, which compared pembrolizumab plus pemetrexed and platinum chemotherapy with chemotherapy alone for the first-line treatment of patients with metastatic (stage IV), non-squamous, NSCLC with negative EGFR and ALK status. Eligible patients were aged at least 18 years, had an Eastern Co-operative Oncology Group (ECOG) performance status 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.

All patients received pemetrexed 500mg/m^2 plus investigator's choice of platinum therapy (cisplatin 75mg/m^2 or carboplatin area under the concentration-time curve [AUC] 5mg/mL/minute) intravenously every three weeks for four cycles, followed by pemetrexed maintenance 500mg/m^2 every three weeks for up to 35 cycles. In addition, patients were randomised in a 2:1 ratio to receive pembrolizumab (n=410) or placebo (n=206) every three weeks for up to 35 cycles, with stratification for PD-L1 expression (TPS ≥1% versus <1%), choice of platinum medicine (cisplatin versus carboplatin), and smoking history (never versus former or current). Treatment was continued until disease progression, unacceptable toxicity, investigator decision, or patient withdrawal. If toxicity was associated with a specific medicine then that medicine could be discontinued. Patients randomised to placebo, who had confirmed disease progression on blinded central radiologic review, were eligible to crossover to receive pembrolizumab monotherapy.[3]

The primary outcomes were overall survival (defined as time from randomisation until death from any cause) and progression free survival (PFS) (defined as time from randomisation to disease progression, as assessed via independent central radiologic review according to RECIST 1.1, or death from any cause, which ever occurred first). The company provided results from an interim analysis (data cut-off 21 September 2018) including subgroup analysis in patients with PD-L1<50% TPS and these were the data considered by the SMC committee. After a median follow-up of 18.7 months, median overall survival was 22.0 months in the pembrolizumab group and 10.7 months in

the placebo group, hazard ratio 0.56 (95% Confidence Interval [CI]: 0.45 to 0.70).[4] We are unable to present the rest of the results considered by the SMC committee as the company considers that they are confidential.

At an earlier interim analysis (data cut-off November 2017) after a median follow-up of 10.5 months, overall survival and PFS were both significantly longer in the pembrolizumab group compared with the placebo group in the intention to treat population. [1-3] Results for the primary outcome of overall survival and PFS are shown in Table 1 below.

Table 1: Primary outcomes in the pembrolizumab and placebo groups of KEYNOTE-189 at first interim analysis (data cut-off November 2017) in the intention to treat population[1-3]

	Pembrolizumab + pemetrexed + platinum (n=410)	**Placebo + pemetrexed + platinum (n=206)**
Overall survival		
Number of events	127	108
Median overall survival (months)	not reached	11.3
Hazard ratio (95% CI)	0.49 (0.38 to 0.64) p<0.001	
Estimated overall survival rate at 6 months	85%	78%
Estimated overall survival rate at 12 months	69%	49%
Progression free survival		
Number of events	244	166
Median progression free survival (months)	8.8	4.9
Hazard ratio (95% CI)	0.52 (0.43 to 0.64) p<0.001	
Estimated progression free survival rate at 6 months	66%	48%
Estimated progression free survival rate at 12 months	34%	17%

The secondary outcome was objective response rate (ORR), defined as the percentage of patients with a confirmed complete or partial response, assessed according to RECIST 1.1 by blinded independent radiologic review. At the interim analysis, the ORR was significantly higher in the pembrolizumab than placebo group: 48% (195/410) versus 19% (39/206); difference of 28% (95% CI: 21 to 35%). The ORR included a complete response in 0.5% of patients in both groups.[3]

In KEYNOTE-189, quality of life was assessed as an exploratory outcome using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the supplemental lung cancer specific items, EORTC QLQ-Lung Cancer 13 (LC13), and the EuroQol Group (EQ) 5D visual analogue scale.[5] The EQ-5D VAS scores (range 0 to 100, with higher score indicating better quality of life) were similar in the pembrolizumab and

placebo groups at baseline and at weeks 12 and 21. The EORTC QLQ-C30 scores were also similar in the pembrolizumab and placebo groups at baseline and at weeks 12 and 21. The between group differences in both measures numerically favoured pembrolizumab at weeks 12 and 21.[6]

Supportive evidence is available from a single cohort of the KEYNOTE-021 study which assessed adding pembrolizumab to four cycles of pemetrexed plus carboplatin chemotherapy in patients with stage IIIB and IV, non-squamous NSCLC. All patients received optional pemetrexed for 24 months and patients in the pembrolizumab group continued pembrolizumab for 24 months. The primary outcome was ORR defined as patients with complete or partial response as per RECIST 1.1 assessed by blinded independent central review. At the data cut-off of August 2016 and a median follow-up of 10.6 months, ORR was 55% (33/60) of patients in the pembrolizumab combination group compared with 29% (18/63) of patients in the chemotherapy alone group; difference 26% (95% CI: 9 to 42), p=0.0016. At an updated analysis (December 2017), after a median follow-up of 23.9 months, ORR was 57% (34/60) in the pembrolizumab combination group and 30% (19/63) in the chemotherapy alone group; difference 26% (95% CI: 8.9 to 42), p=0.0016. Median PFS was 24.0 months and 9.3 months respectively (HR 0.53 [95% CI: 0.33 to 0.86], p=0.005) and median overall survival had not been reached in the pembrolizumab combination group and was 21.1 months in the chemotherapy alone group (HR 0.56 [95% CI: 0.32 to 0.95], p=0.015).[7 8]

The submitting company presented a network meta-analysis (NMA) to compare pembrolizumab in combination with pemetrexed and platinum with other chemotherapy regimens used for the treatment of NSCLC, including gemcitabine, vinorelbine, paclitaxel or docetaxel plus platinum and paclitaxel plus bevacizumab plus platinum. This analysis suggested that pembrolizumab combination therapy was superior to alternatives in terms of PFS and overall survival. Relative safety was not compared.

*Other data were also assessed but remain confidential**

Summary of evidence on comparative safety

The company provided safety information from an interim analysis (data cut-off 21 September 2018), however we are unable to present these results as the company considers that they are confidential. Safety was assessed using the "as treated" population (n=607), which was defined as all patients who received at least one dose of study medication. At an earlier interim analysis (data cut-off November 2017), the mean duration of treatment was 7.4 months in the pembrolizumab group compared with 5.4 months in the placebo group. Patients in the pembrolizumab treatment group had longer exposure to study medicine than those in the placebo group.[3]

In the "as treated" population, a total of 99.8% (404/405) of patients randomised to pembrolizumab and 99.0% (200/202) of patients randomised to placebo reported an adverse event (AE) of any grade. Grade 3, 4, or 5 AEs were reported by 67% (272/405) and 66% (133/202) of patients randomised to pembrolizumab and placebo respectively. In the pembrolizumab group,

28% (112/405) of patients discontinued any treatment component due to an AE compared with 15% (30/202) of patients in the placebo group.[3, 6]

The most frequently reported adverse events of any grade in the pembrolizumab and placebo groups (data cut-off September 2017) were: nausea (56% and 52%), anaemia (46% and 47%), fatigue (41% and 38%), constipation (35% and 32%), diarrhoea (31% and 21%), decreased appetite (28% and 30%), neutropenia (27% and 24%), vomiting (24% and 23%), cough (21% and 28%), dyspnoea (21% and 26%), asthenia (20% and 24%) and rash (20% and 11%).[3]

Immune-mediated adverse events (data cut-off September 2017) were reported by 23% (92/405) of patients in the pembrolizumab group and 12% (24/202) of patients in the placebo group and these were grade 3, 4, or 5 in 8.9% (36/405) and 4.5% (9/202) of patients respectively. The most commonly reported immune-mediated reactions in the pembrolizumab and placebo groups respectively were: hypothyroidism (6.7% and 2.5%), pneumonitis (4.4% and 2.5%), hyperthyroidism (4.0% and 3.0%), infusion reaction (2.5% and 1.0%), colitis (2.2% and 0%), severe skin reaction (2.0% and 2.5%), nephritis (1.7% and 0%) and hepatitis (1.2% and 0%).[3]

Thirty-nine deaths (data cut-off September 2017) were related to an adverse event; n=27 (6.7%) in the pembrolizumab group and n=12 (5.9%) in the placebo group. Three deaths in the pembrolizumab group were attributed to an immune-mediated pneumonitis.[3]

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

Summary of clinical effectiveness issues

NSCLC can be subdivided into non-squamous cell carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types) and squamous cell (epidermoid) carcinoma. The majority of patients with NSCLC are diagnosed at an advanced stage with either locally advanced (stage III) disease or metastatic (stage IV) disease. Current guidelines recommend that patients with advanced non-squamous NSCLC who are EGFR and ALK mutation negative are treated in the first-line setting with four cycles of cisplatin plus pemetrexed followed by maintenance pemetrexed. [9-11] Pembrolizumab as monotherapy has also been licensed and accepted for use by SMC for patients with metastatic NSCLC with PD-L1 ≥50% and no EGFR or ALK mutations, and for use second-line in patients whose tumours express PD-L1. Use in these setting is restricted to a period of up to two years.

The submitting company has requested that SMC consider use of pembrolizumab in the subgroup of patients with PD-L1 expression <50%, and for use in those whom it has not been possible to evaluate PD-L1 TPS, based on the fact that current treatment options are limited for these patients, and pembrolizumab monotherapy has been accepted by SMC for patients with PD-L1 ≥50%. Pembrolizumab meets SMC end of life criteria.

The company presented results from an updated analysis of the KEYNOTE-189 study. The addition of pembrolizumab to pemetrexed plus platinum chemotherapy significantly improved overall survival and PFS. Supportive results from a cohort of the KEYNOTE-021 study suggested a significant survival benefit when pembrolizumab was added to carboplatin plus pemetrexed after almost two years follow-up.[7, 8] Clinical experts consulted by SMC consider pembrolizumab to be a therapeutic advancement due to the survival benefit.

Quality of life was assessed as exploratory outcomes only during KEYNOTE-189.

KEYNOTE-189 is ongoing and mature overall survival data are awaited. Following confirmed disease progression, patients in the placebo group could crossover to receive pembrolizumab monotherapy which, in addition to any subsequent treatments, may confound later survival data.

In KEYNOTE-189, patients had ECOG performance status of 0 or 1.[3] In clinical practice, there may a number of patients who are unfit to receive platinum based chemotherapy and for these patients the use of pembrolizumab in combination with platinum plus pemetrexed would not be a suitable option.

The results relevant to this resubmission are from a subgroup analysis in patients with PD-L1 <50% and the study may not have been adequately powered for this subgroup.

Patients with PD-L1≥50% are eligible for pembrolizumab monotherapy for first-line treatment. There may be a small number of patients with non-evaluable PD-L1 status who would remain ineligible for treatment with pembrolizumab if the medicine was restricted to the population of patients with PD-L1<50%. The submitting company has requested that SMC also considers patients with non-evaluable PDL1 status in their decision-making.

The company presented a network meta-analysis (NMA) to compare pembrolizumab in combination with pemetrexed and platinum with other chemotherapy regimens used for the treatment of NSCLC. Current guidelines recommend the use of platinum plus pemetrexed for the first-line treatment of patients with non-squamous NSCLC. Since there is direct comparative evidence from KEYNOTE-189, the results of this NMA may be less clinically relevant.

The introduction of pembrolizumab for this indication would add an additional treatment to current standard doublet chemotherapy for patients with advanced non-squamous NSCLC and no EGFR or ALK positive tumours mutations, and PDL1<50%. Treatment with pembrolizumab will require IV infusions every three weeks for up to 35 cycles which will have service and patient implications compared with Scottish clinical practice where four cycles of platinum containing doublet chemotherapy is given. However, these patients may currently also receive maintenance therapy with pemetrexed every three weeks. Clinical experts consulted by SMC considered that the introduction of pembrolizumab for this indication may impact on the service in terms of delivering and managing additional treatment.

*Other data were also assessed but remain 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** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Metastatic non-squamous NSCLC is incurable with a high symptom burden including breathlessness, fatigue and chest pain. These symptoms are difficult to manage and reduce patients' capacity to live independently. There is a substantial impact on the quality of life of patients, carers and family through physical, financial and psychological strain.
- Current treatment options are limited for patients with less than 50% PD-L1 expression. The addition of pembrolizumab to doublet chemotherapy provides a significant survival benefit for patients with no detrimental effect on overall quality of life.
- Currently, these patients would have to wait until second line to receive immunotherapy treatment, however around half of patients treated with doublet chemotherapy are not suitable for another line of treatment following disease progression.
- Family and carers would benefit from an increase in duration of life and improved quality of life, which may enable patients to live independently for longer.

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 7.5% pharmaceutical company funding in the past two years, including from the submitting company. The Scottish Lung Cancer Nurses Forum has received 80% pharmaceutical company funding in the past two years, including 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 considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing pembrolizumab in combination with pemetrexed and platinum chemotherapy against standard of care (SoC) chemotherapy, for the first line treatment of metastatic NSCLC in adults whose tumours have no EGFR or ALK positive mutations. The company has requested SMC consider pembrolizumb for use in patients who have PD-L1 expression levels <50%, and for use in those whom it has not been possible to evaluate PD-L1 TPS. SoC consisted of pemetrexed plus cisplatin or carboplatin, which SMC clinical experts have

considered to be the primary SoC comparator. SMC experts have noted that other combinations are used less frequently in clinical practice.

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 PD-L1<50% subgroup the primary data source for PFS and overall survival estimation was the phase III KEYNOTE-189 comparative study, which used the latest data cut off (Sep 2018). [3] A two-phase piecewise modelling approach was taken. For the first 54 weeks the observed overall survival data from the KEYNOTE-189 study were used, and then separate functions fitted to the data from this time point, consisting of a log normal curve for both the pembrolizumab combination and SoC arms based on statistical and visual fit. The company did not adjust for treatment switching to PD-L1 therapies in the clinical study to reflect expected actual practice subsequent to SoC chemotherapy. For PFS, extrapolation was performed from week 21 with the Weibull function used for both pembrolizumab combination and SoC. The company also provided results for the PD-L1≥50% population, the ITT population and for the PD-L1<50% population (including patients with non-evaluable (NE) PD-L1 status). For the PD-L1≥50%, clinical data were based on the indirect treatment comparison (ITC), whilst KEYNOTE-189 was used for the ITT population and the PD-L1<50% + NE patients).

Utility estimates were based on pooled analysis of the EQ-5D data derived from KEYNOTE-189 study using the latest data cut-off (Sep 2018) according to time to death, regardless of whether the patient had progressed or not. Adverse event 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 adverse events to those who did not.

Resource use in the analysis included medicine acquisition costs for pembrolizumab combination and SoC chemotherapy alone including pemetrexed maintenance therapy in both arms, medicine administration, subsequent second line therapies, adverse event management, and health-state costs (e.g. monitoring, disease management, terminal care relating to progression-free and post-progression patients). PD-L1 test costs have been excluded from the analysis. Dose intensity adjustments were applied. Time on treatment was estimated by fitting parametric functions to the observed clinical study data for time to treatment discontinuation for each treatment arm (exponential function fitted to both the pembrolizumab combination and SoC arms). 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 maximum treatment duration of 12 weeks was assumed for SoC comparator platinum therapy followed by pemetrexed maintenance therapy reflecting the KEYNOTE 189 protocol and clinical practice. Subsequent second-line treatment received was assumed to consist primarily of the use of a PD-L1 therapy (pembrolizumab monotherapy or nivolumab) post- SoC, or docetaxel with nintedanib, and post pembrolizumab combination consisting of docetaxel with nintedanib.

A patient access scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Approximately two thirds of the overall survival benefit is associated with longer time estimated in the post-progression state with pembrolizumab. A cost-offset was associated with lower subsequent therapy costs in the pembrolizumab combination arm, due to the high relative use of PD-L1 therapies assumed after first line SoC chemotherapy.

Table 4: Base case for pembrolizumab combination vs. Standard of Care chemotherapy alone (PD-L1<50% subgroup) with PAS

Technologies	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SoC chemotherapy		-	-
pembrolizumab combination	£40,356	0.99	£40,580

SoC = standard of care, QALY = quality-adjusted life-year, ICER = incremental cost-effectiveness ratio

One way sensitivity analysis demonstrated the base case ICER for pembrolizumab vs. SOC appeared most sensitive to the extrapolation of overall survival, and utility values for longer term survivors (i.e. >360 days). Key scenario analyses are presented in the Tables below for the PD-L1<50% population. The company has also provided results for different subgroups according to PD-L1 status. For the ITT subgroup, pembrolizumab combination resulted in an ICER of £57,552 with PAS. For the PD-L1≥50% subgroup, pembrolizumab combination resulted in an ICER of £78,434 with PAS. For the PD-L1<50% (including non evaluable patients) pembrolizumab combination resulted in an ICER of £43,023 with PAS.

Table 5: Scenario analyses results (PD-L1<50%) with PAS

Scenario	ICER (£/QALY)
OS extrapolation: use of 54 week data and extrapolation based on exponential function (best fitting curve) for both treatment arms	£60,189
Treatment waning: assuming treatment effect stops at 5 years	£43,764
Applying conventional PFS and post progression state utilities	£45,859

OS = overall survival, PFS = progression-free survival, QALY = quality-adjusted life-year, ICER = incremental cost-effectiveness ratio

Table 6: Requested scenario analyses results (PD-L1<50%) with PAS

Scenario	ICER (£/QALY)
Time horizon of 10 years	£48,643
OS: extrapolation using Log-logistic (applied to both arms separately at 54 weeks)	£54,970
Waning of treatment effect: Loss of pembrolizumab effect at 3 years	£47,800
>360 day utility reduced to 0.75	£43,076
Post progression utility reduced to 0.55	£52,078
Removal of prembrolizumab stopping rule	£43,080
Assume 50% use of a PD-L1 as a subsequent therapy post standard of care	£43,762
Combined scenario analysis	£64,202

- Use of Log-logistic curve to extrapolate OS (Log-logistic curve fitted separately to both treatment arms) - Waning of treatment effect: Loss of pembrolizumab effect at 5 years - Applying PFS and post progression state utilities (0.759, 0.55 respectively)	

OS = overall survival, PFS = progression-free survival, QALY = quality-adjusted life-year, ICER = incremental cost-effectiveness ratio

There are some remaining uncertainties with the economic analysis:

- There is uncertainty over the OS benefit estimated for pembrolizumab combination vs SoC due partly to the immaturity of the OS data from the KEYNOTE 189 study. Scenario analyses were requested exploring the use of other parametric functions that seemed also to have a reasonable statistical and visual fit to the observed OS data. The log-logistic curve produced plausible 5 year OS estimates for SoC with 9% of patients were estimated to be alive at this time point. The plausibility of this OS estimate is supported by expert opinion.
- There are some uncertainties over the use of TTD based utility estimates as the base case, or conventional PFS and post progression based utilities which fits the model structure better. In addition, a requested scenario analysis showed some upward ICER sensitivity to assuming a conservative utility value of 0.55 for the post- progression state.
- In order to extract an upper bound, yet plausible ICER, the company was asked to provide a combined scenario analysis which incorporates a number of uncertainties including, extrapolation of OS using the log logistic function, assuming pembrolizumab treatment effect stops at 5 years, use of progression based utilities. These results are presented in Table 6 above.

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 life expectancy in the patient population targeted in the submission was met.

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

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

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 137, Management of lung cancer in February 2014. The guidance recommends that 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. Adding combination systemic anticancer therapy to a tyrosine kinase inhibitor confers no benefit and should not be used.[11]

The National Institute for Health and Care Excellence (NICE) published Lung cancer: diagnosis and management (NG 122) in March 2019.[9] The guidance makes recommendations for patients with no gene mutation or fusion protein and PD-L1<50%. Specifically, the guidance makes the following recommendations for the treatment for stage IIIB and IV non-squamous NSCLC in people who do not have a gene mutation, fusion protein or biomarker:

- see the NICE technology appraisal guidance on pembrolizumab combination and pemetrexed with cisplatin or offer pemetrexed with carboplatin or other platinum doublet chemotherapy (TA557).
- if people do not immediately progress after chemotherapy, see the NICE technology appraisal guidance on pemetrexed maintenance after pemetrexed and pemetrexed maintenance after other platinum doublet chemotherapy.
- on progression after first-line chemotherapy see the NICE technology appraisal guidance on atezolizumab, nivolumab, pembrolizumab and nintedanib with docetaxel or offer docetaxel monotherapy.
- on progression after pembrolizumab combination, see the NICE technology appraisal guidance on nintedanib with docetaxel or offer docetaxel monotherapy.[9]

The European Society for Medical Oncology (EMSO) published a clinical practice guideline on the diagnosis, treatment and follow-up of metastatic NSCLC in 2016.[10] This guidance makes the following recommendations:

- Chemotherapy with platinum doublets should be considered in all stage IV NSCLC patients with EGFR- and ALK-negative disease, without major comorbidities and PS 0-2.
- Platinum-based doublets are the recommended option in all stage IV NSCLC patients with no contraindications to platinum compounds.
- Four cycles of platinum-based doublets followed by less toxic maintenance monotherapy, or four up to a maximum of six cycles in patients not suitable for maintenance monotherapy, are currently recommended.
- In non-squamous tumours and in patients treated with third-generation regimens, cisplatin should be the treatment of choice.

Pemetrexed is preferred to gemcitabine or docetaxel in patients with non-squamous tumours and is restricted to any line of treatment.[10]

Additional information: comparators

pemetrexed plus platinum alone

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
Pembrolizumab **Pemetrexed** **Cisplatin***	**200mg IV infusion on day 1** **500mg/m^2 IV infusion on day 1** **75mg/m^2 IV infusion on day 1**	**5,260** **1,260** **72** **Total 6,592**
Pemetrexed Cisplatin**	500mg/m^2 IV infusion on day 1 75mg/m^2 IV infusion on day 1	1,260 72 Total 1,332

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online/BNF online on 05 July 2019. Costs calculated using the full cost of vials/ampoules assuming wastage, and assuming a body surface area (BSA) of 1.8m^2. Costs do not take any patient access schemes into consideration. *Following four cycles of pembrolizumab plus pemetrexed plus cisplatin, pembrolizumab plus pemetrexed may be given as maintenance therapy on day one of a three-week cycle (cost per cycle=£6,520). **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=£1,260). Cisplatin may be replaced by carboplatin Regimens are for illustrative purposes only; not all regimens have been included. IV= intravenous.*

Additional information: budget impact

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 confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 16 August 2019.

**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: https://www.scottishmedicines.org.uk/media/3572/20180710-release-of-company-data.pdf*

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 medicine 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 NHSScotland 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 NHSScotland 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.