

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

Merck Sharp & Dohme Ltd

11 January 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 full submission assessed under the end of life process

**pembrolizumab (Keytruda®)** is not recommended for 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.

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

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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

**Chairman**  
**Scottish Medicines Consortium**

## 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 EGFR or ALK positive mutations.<sup>1, 2</sup>

## Dosing Information

Pembrolizumab 200mg administered as an intravenous infusion over 30 minutes every 3 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.

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.<sup>1, 2</sup>

## Product availability date

11 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. This blockade potentiates T-cell responses resulting in immune-mediated anti-tumour activity.<sup>1, 2</sup> SMC has previously accepted pembrolizumab for restricted use 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  $\geq 50\%$  tumour proportion score (TPS) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations [SMC 1239/17] and as monotherapy for the treatment of locally advanced or metastatic NSCLC in

adults whose tumours express PD-L1 with a  $\geq 1\%$  TPS and who have received at least one prior chemotherapy regimen [SMC 1204/17]. Both are restricted by a two-year clinical stopping rule. The indication currently under review is for first-line use in combination with pemetrexed and platinum chemotherapy in patients with non-squamous NSCLC whose tumours have no EGFR or ALK positive mutations.

The key evidence of efficacy comes from the pivotal KEYNOTE-189 study. This is an ongoing, randomised, double-blind, phase III study, which compares the addition of pembrolizumab to pemetrexed plus platinum chemotherapy 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  $500\text{mg}/\text{m}^2$  plus investigator's choice of platinum therapy (cisplatin  $75\text{mg}/\text{m}^2$  or carboplatin area under the concentration-time curve [AUC]  $5\text{mg}/\text{mL}/\text{minute}$ ) intravenously every three weeks for four cycles, followed by pemetrexed maintenance  $500\text{mg}/\text{m}^2$  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  $\geq 1\%$  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.<sup>3</sup>

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). At the time of interim analysis (data cut-off November 2017), after a median follow-up of 10.5 months, there had been 235 deaths and 410 events of progression or death in the ITT population. Both overall survival and PFS were significantly longer in the pembrolizumab group compared with the placebo group.<sup>3</sup> Results for the primary outcome of overall survival and PFS are shown in Table 1 below.

**Table 1: Primary outcomes in the KEYNOTE-189 study at first interim analysis (data cut-off November 2017) in the intention to treat population<sup>1-3</sup>**

	<b>Pembrolizumab + pemetrexed + platinum (n=410)</b>	<b>Placebo + pemetrexed + platinum (n=206)</b>
<b>Overall survival</b>		
Number of events	31% (127/410)	52% (108/206)
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%
<b>Progression free survival</b>		
Number of events	60% (244/410)	81% (166/206)
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%

CI = confidence interval

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.<sup>3</sup>

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.<sup>4</sup> 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.<sup>5</sup>

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).<sup>6,7</sup>

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

## Summary of evidence on comparative safety

Safety was assessed in the “as treated” population (n=607), defined as all patients who received at least one dose of study medication. At the interim analysis, 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.<sup>3</sup>

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.<sup>3,5</sup>

The most frequently reported adverse events of any grade in the pembrolizumab and placebo groups 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%).<sup>3</sup>

Immune-mediated adverse events 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%).<sup>3</sup>

Thirty-nine deaths 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.<sup>3</sup>

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

## Summary of clinical effectiveness issues

NSCLC can be subdivided into non-squamous 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 or in patients with squamous disease, cisplatin/carboplatin and a third generation agent (docetaxel, gemcitabine, paclitaxel or vinorelbine).<sup>8,9</sup> Pembrolizumab is licensed for use as monotherapy in patients with metastatic NSCLC whose tumours have high PD-L1 expression (TPS  $\geq$ 50%) and no EGFR and ALK mutations. This has been accepted for use by SMC, restricted to a two year stopping rule. The current submission, for use in combination with pemetrexed and platinum for the first-line treatment of patients with non-squamous NSCLC and no EGFR or ALK positive mutations, is irrespective of PD-L1 expression levels.<sup>1,2</sup> Pembrolizumab meets SMC end of life criteria.

Results for the pivotal KEYNOTE-189 study are currently only available from interim analysis after a median follow-up of 10.5 months. The addition of pembrolizumab to pemetrexed plus platinum chemotherapy significantly improved PFS, providing an additional 3.9 months of PFS. The study is ongoing and median overall survival has not yet been reached in the pembrolizumab group but was significantly longer than in the placebo group, median of 11.3 months.<sup>3</sup> Mature survival data are awaited. 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.<sup>6,7</sup>

On confirmed disease progression, patients in the placebo group could cross over to pembrolizumab. At the time of the interim analysis, 33% (67/206) of placebo patients had crossed over to pembrolizumab monotherapy and an additional 8.7% (18/206) of patients had received immunotherapy outwith the study. Overall, 30% (125/410) of pembrolizumab patients and 47% (96/206) of placebo patients, including those who had crossed over, had received at least one subsequent therapy either within or outwith the study.<sup>3,10</sup> Crossover and subsequent treatments may confound further survival data.

In KEYNOTE-189, patients had ECOG performance status of 0 or 1.<sup>3</sup> In clinical practice, there may be 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.

Quality of life was assessed as exploratory outcomes only during KEYNOTE-189. Results are only available to 21 weeks and were similar in both groups.<sup>5</sup>

Current guidelines recommend the use of cisplatin plus pemetrexed for the first-line treatment of patients with non-squamous NSCLC.<sup>8,9</sup> In KEYNOTE-189, the choice of platinum agent was determined by the investigator and only 28% of patients received cisplatin with the remainder receiving carboplatin. However, subgroup analyses suggested that the treatment effect was larger in patients treated with cisplatin.<sup>3</sup>

Subgroup analyses of KEYNOTE-189 found that adding pembrolizumab to platinum plus pemetrexed resulted in a consistent treatment effect across all subgroups of PD-L1 expression (TPS<1%; TPS 1 to 49%; TPS≥50%). The relative benefit appeared greatest in the subgroup of patients with TPS≥50%. The hazard ratios for the differences between pembrolizumab and placebo for the TPS<1% (n=190), TPS 1 to 49% (n=186) and TPS≥50% (n=202) subgroups respectively for overall survival were 0.59, 0.55 and 0.42 and for PFS were 0.75, 0.55 and 0.36.<sup>1-3</sup> Pembrolizumab monotherapy is a first-line treatment option for patients with TPS≥50%. The indication under review includes patients with all levels of PD-L1 expression. However, the SPC recommends PD-L1 testing for patients with NSCLC. It recommends that the risk of adverse events with pembrolizumab combination therapy relative to pembrolizumab monotherapy should be considered in patients with non-squamous NSCLC whose tumours have high PD-L1 expression and the benefit/risk ratio of the combined therapy evaluated on an individual basis.<sup>1,2</sup> There is no direct evidence comparing pembrolizumab combination therapy with pembrolizumab monotherapy in these patients.

The submitting company presented a matched adjusted indirect comparison of pembrolizumab in combination with pemetrexed and platinum chemotherapy with pembrolizumab monotherapy in patients with non-squamous NSCLC and strong PD-L1 expression levels (TPS ≥50%). The indirect comparison included relevant subgroups of patients from two studies and adjusted for differences between the study populations. The treatments were then compared for PFS and overall survival using the Bucher method. The results indicated that pembrolizumab in combination with platinum and pemetrexed was numerically favoured over pembrolizumab monotherapy in terms of both outcomes in patients with metastatic non-squamous NSCLC with PD-L1 TPS ≥50%. However, wide credible intervals for the hazard ratios indicate no evidence of a difference between the treatments and reflect the uncertainty in the results. Despite the adjustment to balance the patient populations, there were a number of remaining differences which may affect the results including crossover and subsequent treatment (the effect of which was investigated in sensitivity analyses) and the use of pemetrexed maintenance therapy. There were also differences in the

durations of available follow-up with available data from the KEYNOTE-189 currently immature. The indirect comparison did not compare relative safety and this may be clinically relevant when considering the risk/benefit of the two treatments.

The submitting company also 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 better than alternatives in terms of PFS and overall survival. Relative safety was not compared. However current guidelines recommend the use of platinum plus pemetrexed for the first-line treatment of patients with non-squamous NSCLC and since there is direct comparative evidence from KEYNOTE-189, the results of the 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. 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.

### 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 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, 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. SoC consisted of pemetrexed plus platinum alone, which SMC clinical experts have considered to be the primary SoC comparator, although the company also performed comparisons with a range of other platinum- based combination chemotherapy regimens. However, SMC clinical expert feedback is the 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 comparison with SoC the primary data source for PFS and overall survival estimation was the phase III KEYNOTE-189 comparative study.<sup>3</sup> A two-phase piecewise modelling approach was taken. For the first 28 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, using an exponential function for both the pembrolizumab combination and SoC groups based on statistical and visual fit. In the base case analysis, 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 comparisons with other platinum based combination therapies were based on an NMA described in the clinical effectiveness section above.

Utility estimates were based on a pooled analysis of the EQ-5D data derived from KEYNOTE-189 study 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, PD-L1 testing, and health-state costs (e.g. monitoring, disease management, terminal care relating to progression-free and post-progression patients). 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 for pembrolizumab combination, and Weibull 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). 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, and post pembrolizumab combination consisting predominantly of docetaxel with/without nintedanib or carboplatin + pemetrexed.

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. The corresponding base case incremental cost-effectiveness ratio (ICER) with the PAS discount is £48,551 per quality-adjusted life-year (QALY), based on an incremental cost of £43,104 and a QALY gain of 0.89 (Table 2). 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 2: Base case results for pembrolizumab combination vs. Standard of Care chemotherapy alone (with PAS)**

Analysis	Treatment	Total costs	Total QALYs	Incremental cost £	Incremental QALYs	ICER
Base case	Pembrolizumab combination	£85,431	1.81	£43,104	0.89	£48,551
	SoC	£42,327	0.92			

One way sensitivity analysis demonstrated the base case ICER for pembrolizumab combination versus SoC appeared most sensitive to the extrapolation of overall survival, and utility values for longer term survivors (i.e. >360 days). The ICERs for pembrolizumab combination versus other doublet chemotherapy regimens based on the NMA and the results of key scenario analyses are presented in Table 3. Other scenario analyses considering a range of time points for PFS extrapolation, (11 and 31 weeks), SoC chemotherapy based on Scottish market shares (rather than clinical study proportions), treatment arm specific utilities, no age related disutility, alternative dose regimen for pembrolizumab based on weight 2mg/kg rather than fixed dose, 2<sup>nd</sup> line pembrolizumab monotherapy assumed used in 7% of patients as per clinical study, only had a relatively small impact on the ICER.

**Table 3: Results for comparisons with other doublet chemotherapy comparators and key scenario analyses**

Scenario Analysis	ICER with PAS
Alternative comparator: platinum + paclitaxel	£56,286
Alternative comparator: platinum + gemcitabine	£60,791
Alternative comparator: platinum + vinorelbine	£65,227
Alternative comparator: platinum + docetaxel	£80,661
Extrapolation of OS from 38 weeks	£58,486
Extrapolation of OS from 18 weeks	£43,292
OS extrapolation: parametric function based on lognormal (2 <sup>nd</sup> best fitting) for both treatment arms	£52,538
Treatment waning: assuming treatment effect stops at 5 years	£54,599
Applying PFS and post progression state utilities	£54,734
OS extrapolation: log logistic	£87,223
OS extrapolation: Weibull	£130,649
Treatment waning: assuming treatment effect stops at 4 years	£58,559
Assuming post progression utility of 0.55	£61,092
Assuming 50% use of PD-L1 therapies as subsequent therapies after SoC	£54,764

**Table 4: Results by PD-L1 subgroup**

Subgroup	ICER with PAS
PD-L1 ≥50% versus pembrolizumab monotherapy (assuming 100% docetaxel use as subsequent therapy)	£47,793
PD-L1 <50% population versus SoC	£47,460
PD-L1 1%-49% versus SoC	£40,323
PD-L1<1% versus SoC (using 2 stage treatment switching adjustment)*	£73,049
PD-L1<1% versus SoC (using IPCW treatment switching adjustment)*	£90,129

SoC=standard of care, IPCW= inverse probability of censoring weights ,\*OS adjustment due to treatment switching to a PD-L1 after SoC performed as use of PD-L1 therapies in this sub-group is not expected in clinical practice post first line chemotherapy

There were a number of issues and uncertainties with the economic analysis:

- Feedback from SMC clinical experts has indicated that the appropriate comparator to pembrolizumab combination for patients with PD-L1 expression ≥50% would be pembrolizumab monotherapy, and SoC chemotherapy is used in patients with PD-L1 expression <50%. On request the company provided economic analyses for PD-L1 subgroups against these comparators. For the comparison with pembrolizumab monotherapy there were limitations in the matched adjusted indirect treatment comparison used, including wide credible intervals for the pembrolizumab combination versus monotherapy HR for OS and no assessment of relative safety (see clinical effectiveness issues section above). Hence, the cost-effectiveness results for the PD-L1 ≥50% subgroup are uncertain.
- For the <50% PD-L1 subgroups the estimated ICERs are significantly higher for the <1% PD-L1 expression subgroup, which are also sensitive to the method used for adjustment for

treatment switching (Table 4). While the subgroup analysis showed pembrolizumab combination may be more cost-effective in patients with PD-L1 expression 1% - 49%, no sensitivity analysis was provided to explore the range of uncertainty surrounding the subgroup analysis estimates.

- There is uncertainty over the OS benefit estimated for pembrolizumab combination versus SoC due partly to the immaturity of the OS data from the KEYNOTE 189 study. The scenario analysis assuming that the pembrolizumab treatment effect stops at 5 years and a scenario applying a parametric function to the observed OS data from a later time point increased the ICER (Table 3). Further scenario analysis was requested exploring the use of other parametric functions that seemed also to have a reasonable statistical and visual fit to the observed OS data. These demonstrated much higher ICERs indicating the uncertainty associated with the extrapolated estimates of OS benefit for pembrolizumab combination therapy (Table 3). Further scenario analyses assuming shorter treatment effect also had an upward impact on the ICER (Table 3).
- There are some uncertainties over the use of TTD based utility estimates as the base case, or conventional PFS and post progression based utilities. Table 3 shows a higher ICER associated with use of the latter approach. In addition, a requested scenario analysis showed some upward ICER sensitivity to assuming a lower but potentially plausible utility of 0.55 for the post progression state (Table 3).

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept pembrolizumab for use in NHS Scotland.

### Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 137, Management of lung cancer in February 2014.<sup>9</sup> 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.<sup>9</sup>

The European Society for Medical Oncology (ESMO) published a clinical practice guideline on the diagnosis, treatment and follow-up of metastatic NSCLC in 2016.<sup>8</sup> 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.

### Additional information: comparators

pemetrexed plus platinum alone; pembrolizumab monotherapy in patients with PD-L1 TPS  $\geq 50\%$ .

### Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
<b>Pembrolizumab Pemetrexed Cisplatin*</b>	<b>200mg IV infusion on day 1 500mg/m<sup>2</sup> IV infusion on day 1 75mg/m<sup>2</sup> IV infusion on day 1</b>	<b>6,597</b>
Pemetrexed Cisplatin**	500mg/m <sup>2</sup> IV infusion on day 1 75mg/m <sup>2</sup> IV infusion on day 1	1,337
Pembrolizumab	200mg IV infusion on day 1	5,260

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online and BNF online on 4 October 2018. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. A body surface area of 1.8m<sup>2</sup> was used for dose calculations, when applicable. Costs for additional vitamin supplements and corticosteroids for pemetrexed have not been included. \* 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

The submitting company estimated there would be 389 patients eligible for treatment with pembrolizumab in year 1, rising to 395 patients in year 5. The estimated uptake rate was 14.5% in year 1 (56 patients), 20.7% in year 2 (81 patients), 20.2% in year 3 (79 patients), 20.3% in year 4 (80 patients), and 20.1% in year 5 (79 patients).

### **Without PAS**

The gross impact on the medicines budget was estimated to be £4.36m in year 1 rising to £6m in year 5. Some medicines were assumed to be displaced resulting in a net budget impact of £3.1m in year 1 rising to £4.4m in year 5.

## References

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3. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, *et al.* Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *New England journal of medicine.* 2018;378(22):2078-92.
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5. Merck Sharp D. CLINICAL STUDY REPORT: A Randomized, Double-Blind, Phase III Study of Platinum+ Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Nonsquamous Non-small Cell Lung Cancer Subjects (KEYNOTE-189). 2018.
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9. Scottish Intercollegiate Guidelines Network. SIGN 137: Management of lung cancer. Available at: <https://www.sign.ac.uk/assets/sign137.pdf>. 2014.
10. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, *et al.* Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *New England journal of medicine.* 2018;378(22):Supp. Appendix.

This assessment is based on data submitted by the applicant company up to and including 09 November 2018.

*\*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](http://www.scottishmedicines.org.uk/About_SMC/Policy)*

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.*