Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2187

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

Merck Sharp & Dohme UK Ltd

9 August 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 medicine process

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

Indication under review: In combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous non-small cell lung cancer (NSCLC) in adults.

SMC restriction: in combination with carboplatin and paclitaxel 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.

Pembrolizumab in combination with platinum based doublet chemotherapy was associated with a progression-free survival and overall survival benefit over platinum based doublet chemotherapy in patients with treatment naïve metastatic squamous NSCLC.

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

Chairman
Scottish Medicines Consortium

Indication

Pembrolizumab, in combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous non-small cell lung cancer (NSCLC) in adults.[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.

Treatment should be administered 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.

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

Product availability date

11 March 2019

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 PD-1 receptor found on 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. The submitting company has requested that SMC considers this product for the full licensed indication, or alternatively when positioned for use in patients with PD-L1 tumour proportion score (TPS) <50%. Pembrolizumab has been previously accepted by SMC as monotherapy for 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.[1, 2]

The evidence supporting the efficacy and safety of pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel (henceforth referred to as pembrolizumab combination) in adult patients with treatment naïve metastatic squamous non-small cell lung cancer (NSCLC) comes from KEYNOTE-407, an international, randomised, double-blind, phase III study. Patients

were required to have previously untreated, confirmed, stage IV squamous NSCLC, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, one or more measurable lesions according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, and adequate organ function.[3, 4]

Patients were randomised equally to receive pembrolizumab 200mg via IV infusion (n=278) or placebo (n=281) every 3 weeks for up to 35 cycles. Both treatment groups received paclitaxel 200mg/m^2 by IV infusion on day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100mg/m^2 by IV infusion on Days 1, 8, 15 of each 21-day cycle for 4 cycles, in combination with carboplatin AUC 6mg/mL/min by IV infusion on day 1 of each 21-day cycle for 4 cycles.[3, 4] Treatment was to continue until radiographic disease progression (as per RECIST version 1.1), unacceptable toxicity, investigator decision to discontinue, withdrawal of patient consent, or for a maximum of 24 months. Administration of pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit, at the discretion of the investigator. Patients randomised to placebo who had confirmed disease progression (on blinded central radiologic review) were eligible to crossover to receive pembrolizumab monotherapy. Randomisation in the study was stratified according to PD-L1 status (TPS ≥1% versus <1%), choice of taxane (paclitaxel versus nab-paclitaxel), and geographic region (East Asia versus the rest of the world).[3-5]

KEYNOTE-407 had two co-primary outcomes: overall survival and progression free survival (PFS). Overall survival was defined as the time between date of randomisation and death due to any cause. PFS was defined as the time between date of randomisation to the date of first progression (independently assessed using RECIST v1.1) or death due to any cause, whichever occurred first.[4] Efficacy analyses were performed in the intention-to-treat population, which included all patients who underwent randomisation. The primary outcomes were analysed by blind and independent review during a pre-specified interim analysis.[3, 4]

The primary PFS analysis was conducted following 349 PFS events in the pembrolizumab combination (152 PFS events) and placebo combination (197 PFS events) groups. At a median follow-up of 8.3 months and 7.4 months respectively, pembrolizumab was associated with a significant improvement in blinded independent central radiologist review (BIRC)-assessed PFS compared with placebo (with both study groups receiving platinum-based doublet chemotherapy) in the ITT population; median PFS 6.4 months and 4.8 months respectively; hazard ratio (HR) 0.56 (95% confidence interval [CI]: 0.45 to 0.70; p<0.001). For the respective groups, Kaplan-Meier estimates of 6-month event-free probability were 64% and 42%. Investigator assessed PFS, as well as the two sensitivity analyses that used alternative censoring rules, produced similar results. In total, 205 deaths had occurred at the time of interim analysis, 85 (31%) in the pembrolizumab group and 120 (43%) in the placebo group. The addition of pembrolizumab to platinum-based doublet chemotherapy was associated with a statistically significant improvement in overall survival; median overall survival 15.9 months versus 11.3 months; HR 0.64 (95% CI: 0.49 to 0.85; p<0.001). Kaplan–Meier estimates of 1 year survival rates were 65% and 48% in the pembrolizumab combination and placebo combination groups respectively.[3, 4]

Secondary outcomes in the KEYNOTE-407 study included: objective response rate (ORR) (defined as the proportion of patients with a confirmed complete or partial response) and duration of response (DOR) (defined as the time from the first documented complete or partial response until disease progression or death).[5] Pembrolizumab combination was associated with an advantage over placebo combination in both ORR and DOR, although the number of complete responses were similar in both groups. Results are detailed in Table 1 below.

Table 1. Secondary Outcomes of KEYNOTE-407 assessed by BIRC in the ITT population.[4]

	Pembrolizumab combination (n=278)	**Placebo combination (n=281)**
Confirmed ORR	58% (161/278)	38% (108/281)
Difference (95% CI)	20% (11% to 28%) p<0.001	
Complete response	1.4% (4/278)	2.1% (6/281)
Partial response	56% (157/278)	36% (102/281)
Median duration of response (months) (range)	7.7 (1.1+ to 14.7+ months)	4.8 (1.3+ to 15.8+ months)

ORR = objective response rate; CI = confidence interval; '+' indicates there is no progressive disease by the time of the last disease assessment.

Subgroup analyses of the primary outcomes broadly supported benefit with pembrolizumab treatment compared with placebo.[3, 5] Pembrolizumab combination was associated with benefits in PFS across all three PD-L1 strata (TPS <1%/1 to 49%/≥50%), with larger relative treatment effects observed with increasing levels of PD-L1 expression. Overall survival was broadly similar in each PD-L1 stratum. A total of 12 patients (2.1%) in the study had an unknown PD-L1 status and were not included in this subgroup analysis.[3, 4]

Health Related Quality of Life (HRQoL) was assessed as an exploratory endpoint using three questionnaires; The European Organisation for Research and Treatment of Cancer (EORTC) quality of life 30 item questionnaire (QLQ-C30) was supplemented with a lung cancer specific module (QLQ-LC13), and the EuroQoL-5D (EQ-5D) questionnaire was used to characterise health utilities. HRQoL appeared to be maintained when pembrolizumab was added to chemotherapy treatment.[4]

The submitting company presented two indirect treatment comparisons (ITC) that compared pembrolizumab combination against several platinum based chemotherapy regimens (ITC1) and against pembrolizumab monotherapy (ITC2) in patients with previously untreated metastatic NSCLC. The most relevant network meta-analysis (NMA) presented within ITC1 used the squamous population (irrespective of PD-L1 expression), and combined different platinum nodes. Three studies were included in this analysis.[3, 6-9] Key outcomes for both ITCs were PFS and overall survival; studies used in each ITC had similar PFS and overall survival definitions as the KEYNOTE-

407 study. For overall survival, pembrolizumab combination was likely to be superior to platinum plus paclitaxel/nab-paclitaxel and cisplatin plus docetaxel. The survival benefit of pembrolizumab combination was likely to be similar to cisplatin plus gemcitabine. With regards to PFS, pembrolizumab combination was likely to be superior to all the interventions assessed; versus platinum plus paclitaxel/nab-paclitaxel, versus cisplatin plus docetaxel, and versus cisplatin plus gemcitabine.

ITC2 utilised the Bucher method to compare pembrolizumab combination with pembrolizumab monotherapy in patients with previously untreated squamous NSCLC with PD-L1 TPS ≥50%. Two studies were included in the analysis: KEYNOTE-407 and KEYNOTE-042,[5, 10] with the chemotherapy groups of both studies being used as an anchor point. The results suggested there was no significant difference between pembrolizumab combination and pembrolizumab monotherapy.

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

Summary of evidence on comparative safety

The EMA noted that the increased toxicity observed with pembrolizumab use was consistent with what has previously been shown in non-squamous NSCLC, and that no new safety concerns had been highlighted throughout the study.[4]

In the KEYNOTE-407 study, safety was assessed using the "as treated" population (n=558), which was defined as all patients who received at least one dose of study medication. At the interim analysis cut-off, the median duration of treatment in the pembrolizumab combination group was 169 days and in the placebo combination group was 127 days. Any treatment-related adverse event (AE) was reported by 95% of patients in the pembrolizumab combination group (n=278) and 89% in the placebo group (n=280). In the pembrolizumab combination and placebo combination groups respectively, the proportion of patients reporting a grade 3 or higher AE was 70% versus 68%, patients with a reported serious AE was 41% versus 38%, and patients discontinuing any treatment component due to an AE was 23% versus 12%.[3, 4] The most frequently reported AEs of any grade with a incidence >20% in the pembrolizumab combination group versus the placebo group were: anaemia (53% versus 52%), alopecia (46% versus 36%), neutropenia (38% versus 33%), nausea (36% versus 32%), thrombocytopenia (31% versus 23%), diarrhoea (30% versus 23%), decreased appetite (24% versus 29%), constipation (23% versus 22%), fatigue (23% versus 26%), asthenia (22% versus 21%), arthralgia (20% versus 14%) and peripheral neuropathy (20% versus 16%).[3]

Immune-mediated AEs and/or infusion reactions were reported by 29% of patients in the pembrolizumab combination group and 8.6% of patients in the placebo combination group and these were grade 3 or more in 11% and 3.2% of patients respectively. The most commonly reported immune-mediated or infusion reactions in the pembrolizumab combination and placebo combination groups respectively were: hypothyroidism (7.9% versus 1.8%), hyperthyroidism (7.2%

versus 0.7%), pneumonitis (6.5% versus 2.1%), infusion reaction (2.9% versus 2.1%), colitis (2.5% versus 1.4%), hepatitis (1.8% versus 0%), severe skin reaction (1.8% versus 0.4%), hypophysitis (1.8% versus 0%), thyroiditis (1.1% versus 0%), and nephritis (0.7% versus 0.7%).[3]

Summary of clinical effectiveness issues

Lung cancer is the leading cause of cancer death, accounting for 18% of the total cancer deaths worldwide. More than 80% of lung cancer cases are NSCLC, and of these around 10 to 15% can be classified as squamous NSCLC. Squamous NSCLC can be particularly challenging to treat as patients are characteristically older, at an advanced stage of disease at presentation, and may also have comorbidities such as heart disease and chronic obstructive pulmonary disease. Five year survival rates for patients with metastatic NSCLC are estimated to be approximately 6%.[4, 10] There are two broad treatment options for squamous NSCLC patients: pembrolizumab monotherapy and platinum-based doublet chemotherapy. Pembrolizumab monotherapy is the first-line treatment option for patients who have PD-L1 TPS ≥50% with no EGFR or ALK positive tumour mutations, and has been accepted for use by SMC restricted to a two year stopping rule. In patients whose tumour has <50% PD-L1 TPS, or the tumour is non-evaluable, doublet chemotherapy is the current mainstay; a platinum based agent (cisplatin or carboplatin) is used in combination with a third generation cytotoxic (gemcitabine, vinorelbine, or taxanes) for between 4 to 6 cycles of treatment. No particular regimen has demonstrated superior efficacy over the other regimens, and choice is based on medicine toxicity profiles.[4, 11]

The submitting company has requested that SMC considers pembrolizumab for the full licensed indication, or alternatively when positioned for use in patients with PD-L1 TPS <50%. In the key phase III study KEYNOTE-407, median overall survival with pembrolizumab combination was 15.9 months.[3] Pembrolizumab meets SMC end of life criteria.

Pembrolizumab was associated with a statistically significant advantage over placebo, both in combination with platinum based doublet chemotherapy, for PFS in treatment naïve metastatic squamous NSCLC patients. This PFS benefit was observed across almost all subgroups, and various sensitivity analyses including alternative censoring strategies and investigator assessed PFS were all supportive of the primary analysis. Overall survival data were supportive however, further mature efficacy data are awaited. The Committee for Medicinal Products for Human Use (CHMP) have requested that further post-authorisation data be provided when available. Survival data may be confounded by patients in the placebo combination group crossing over to pembrolizumab monotherapy.[4]

Molecular testing in squamous NSCLC is not usually required, unless patients have mixed histology (adenosquamous) and/or a light or non-existent smoking history.[4, 11] In KEYNOTE-407, patients with adenosquamous NSCLC and/or a light or non-existent smoking history were not tested for EGFR or ALK mutations. In total, 41 (7.3%) of patients in the study had never smoked, and 13 patients (2.3%) had adenosquamous histology. It is not known how many patients had EGFR or

ALK mutations in the study. Consequently, it is not clear how effective pembrolizumab combination treatment is for patients with EGFR or ALK mutations.[4]

Study patients had an ECOG performance status of 0 or 1, therefore it is not known if the study results can be extrapolated to patients with poorer performance status.

In KEYNOTE-407 there was an apparent trend toward reduced efficacy of pembrolizumab combination in the elderly population. This trend was particularly apparent in the 75 to 85 years subpopulation, although patient numbers were small (n=62).The EMA acknowledges that data are limited, and have included a warning in the SPC stating that the benefit/risk of using pembrolizumab combination should be considered on an individual basis for elderly patients.[4]

The active comparator used in KEYNOTE-407 was a combination of placebo, carboplatin, and either paclitaxel or nab-paclitaxel. Nab-paclitaxel is currently not recommended for use in Scotland, but 60% and 40% of all patients in the respective treatment groups received this treatment.[4] A previous study that investigated the use of nab-paclitaxel in NSCLC found that it was non-inferior to paclitaxel when given in conjunction with carboplatin.[12] Therefore, the use of nab-paclitaxel in the study is not expected to impact on the generalisability of results to Scottish practice. The platinum containing doublet chemotherapy used in KEYNOTE-407 is an appropriate and relevant comparator for patients with <50% PD-L1 TPS. However, for patients with ≥50% PD-L1 TPS the use of pembrolizumab monotherapy has largely superseded traditional chemotherapy, following results from KEYNOTE-024. Following the market authorisation of pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel for first-line treatment of metastatic squamous NSCLC, the EMA have updated the SPC, stating that patients with high PD-L1 TPS (≥50%) should be given pembrolizumab combination or pembrolizumab monotherapy based upon individual risk/benefit assessment.[1,2,13]

Health Related Quality of Life (HRQoL) data from KEYNOTE-407 appeared to suggest that the addition of pembrolizumab to standard chemotherapy did not impact on quality of life for patients, despite the unfavourable toxicity profile that was observed. However, HRQoL data wereonly collected up to week 18 of treatment and pembrolizumab can be continued for up to 2 years.[4]

There were some relevant limitations to the indirect comparisons presented by the submitting company. The number of studies used in both ITCs was low. In ITC1 (pembrolizumab combination versus various chemotherapy regimens), the studies included in the analysis varied considerably in terms of date of publication, ranging from 2003 to 2018. Further potential heterogeneity in ITC1 came from the CTONG-1002, which varied in terms of study design (phase 2), study population (all Chinese population), and primary outcome (ORR). Differences in the efficacy results of the control treatment groups suggest that heterogeneity exists between studies, affecting both ITCs. The data used in ITC2 (pembrolizumab combination versus pembrolizumab monotherapy), taken from KEYNOTE-407 and KEYNOTE-042, were immature, and the sample sizes used in the analysis were small as the ≥50% PD-L1 TPS subpopulation was used. Lastly, both ITCs did not assess safety or

patient reported outcomes which could have been informative. Despite these limitations, the submitting company's claims of likely superior PFS against standard platinum based doublet regimens seem reasonable and is supported by the direct evidence presented. No evidence of a difference in treatment effect between pembrolizumab combination and pembrolizumab monotherapy seems credible.

Clinical experts consulted by SMC consider pembrolizumab to be a therapeutic advancement due to the associated survival benefit however they also noted the toxicities associated with combination therapy that would need to be managed.

Patient and clinician engagement (PACE)

- Metastatic squamous NSCLC is a devastating, incurable illness with a short life expectancy of under a year in the majority of patients. Symptoms can be very difficult to manage and include breathlessness, weight loss, and chest pain. In addition, there is a major psychological toll on patients with metastatic squamous NSCLC.
- There is a large unmet need for effective treatments in metastatic squamous NSCLC, especially for the PD-L1 <50% population. Patients with PD-L1 <50% presently receive platinum-based doublet chemotherapy, which provides limited benefit at the expense of notable toxicity. Due to these treatment toxicities and time spent in hospital clinics many patients opt not to have treatment at this stage.
- The clinical benefits associated with pembrolizumab plus chemotherapy (i.e. improved progression free survival and overall survival) will translate into quality of life benefits for both patients and family members. Following treatment, patients are expected to remain healthy and independent for longer, and in some patients may be able to continue work or care for young family members. By bringing pembrolizumab further forward in the treatment pathway, more patients would be eligible to benefit from the treatment.
- The addition of pembrolizumab to chemotherapy may be associated with increased toxicity, but this does not concern patients, as the opportunity for prolonged survival is highly valued.
- Although patients in the PD-L1 <50% population will gain the most from access to pembrolizumab plus chemotherapy, there are some scenarios where pembrolizumab plus chemotherapy would be advantageous in the PD-L1 ≥50% population also (e.g. aggressive forms of NSCLC that require quick control). In general, pembrolizumab plus chemotherapy will be used in fitter patients who are able to tolerate the combination therapy.

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 submitting company presented a cost-utility analysis comparing pembrolizumab plus paclitaxel and carboplatin combination versus paclitaxel and carboplatin combination (SoC) for advanced squamous NSCLC where patients have not received prior systemic chemotherapy, with TPS<50%. The cost-effectiveness analysis was based on the relevant sub-group of KEYNOTE-407. The submitting company did provide supplementary analyses to consider the study's overall population, and a further comparison versus pembrolizumab monotherapy in patients with TPS≥50%. However, given issues with the robustness of the evidence base with these supplementary analyses, only the company base case in the TPS<50% was considered relevant for decision-making and considered in detail here.

The cost-effectiveness analysis used a three-state partitioned survival model, with states of progression-free survival (PFS) and post-progression, and death, over a lifetime (30 years) time horizon. Pembrolizumab combination was considered as per the licensed dosing regimen. KEYNOTE-407's protocol mandated a maximum of 2 years treatment and this stopping rule was applied in the model. The composition of SoC was based on KEYNOTE-407 in the base case (60.1% paclitaxel, 30.9% nab-paclitaxel), with 100% paclitaxel applied in scenario analysis. The composition affected medicine acquisition costs only. Patients entering the analysis were assumed to be 65 years of age with a body surface area of 1.88m^2 based on the clinical study.

To estimate long term survival, parametric distributions for PFS and overall survival (OS) were investigated and the projected survival curves were assessed. The submitting company judged that all such curves provided clinically implausible SoC OS outcomes. As such, alternative data sources were considered with which to fit SoC OS, resulting in adoption of long-term hazards based on SEER data from 1992-2014. For the base case analysis KEYNOTE-407 Kaplan-Meier data from the SoC arm were used for the first 12 months followed by SEER based annual mortality estimates. In the pembrolizumab combination model arm relative risks (RR) were applied to the SoC data for long term survival modelling. The RR was estimated as 0.58 (0.38-0.87) based on months 7-12 survival in KEYNOTE-407. An alternative scenario based on parametric extrapolation was included in analyses. This scenario used a cut-point of 19 weeks for use of Kaplan-Meier data, followed by loglogistic extrapolation. A further scenario explored cessation of OS treatment benefit after three to five years.

For PFS, Kaplan-Meier data were used until week 26 in both arms, followed by parametric functions. Separately fitted models were employed for each arm. The lognormal distribution was selected as producing the more plausible extrapolated decline in PFS over time having also taken account of statistical goodness of fit. Time on treatment was modelled based on Kaplan-Meier

data with generalized gamma extrapolation, though extrapolation was not applied to the SoC arm as the Kaplan-Meier had fallen to zero due to maximum treatment duration limits (12 weeks).

The model considered an extensive array of grade 3+ AEs which occurred in at least 5% of patients in either treatment arm of KEYNOTE-407 plus grade 2 diarrhoea (consistent with previous SMC appraisals).

Health state utilities for the model were based on KEYNOTE-407 EuroQol EQ-5D data, with estimates derived according to time to death. Estimates were pooled across arms for the base case based on the absence of statistically significant differences between arms, though a minor difference was applied by treatment arm for AEs. An adjustment for general population age-related decrements was applied.

Costs included medicine acquisition and administration costs, including those related to subsequent therapies, monitoring and management of disease, AEs and terminal care. Following progression, aggregate costs for subsequent therapies were assigned conditional on treatment arm. Greater subsequent treatment costs are applied to the SoC arm, reflecting more intense usage in KEYNOTE-407. Average 'one-off' costs of subsequent treatments for each arm were calculated by weighting the proportions of patients receiving each subsequent treatment and the relevant unit costs and average treatment durations. Monitoring and disease management costs were based on a published study; costs for progressive disease were applied only to patients who progress when no active subsequent treatment was received following first line therapy.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland.

For the base case comparison of pembrolizumab plus paclitaxel and carboplatin combination versus paclitaxel and carboplatin combination, the base case incremental cost-effectiveness ratio (ICER) incorporating the PAS discount is £30,768, as shown in table 3.

Table 3. Results base-case: pembrolizumab combination versus paclitaxel and carboplatin combination (pembrolizumab at PAS discount), TPS<50%

Technologies	Total			Incremental		ICER (£/QALY)
	Costs (£)	Life year gained (LYG)	Quality adjusted life year (QALYs)	Costs (£)	QALYs	
SOC	28,121	1.74	1.25			
Pembrolizumab combination	80,052	4.00	2.94	51,931	1.69	30,768

The most sensitive parameters in one-way analysis were OS RR vs chemotherapy, utility for time to death >360 days, and dose intensity/time on treatment for pembrolizumab and the discount rate applied to health benefits. According to scenario analyses the ICER was sensitive to

parametric extrapolation of OS (compared to a base case Kaplan-Meier with SEER extrapolation), timing of Kaplan-Meier cut-off, and assuming treatment effect stops within 5-years.

Table 4. Scenario analyses: pembrolizumab combination versus paclitaxel and carboplatin combination (pembrolizumab at PAS discount), TPS<50%

Scenario		Inc. costs (£)	Inc. QALYs	ICER (£)
	Base	51,931	1.69	30,768
1	Parametric extrapolation OS cut-off – 19 weeks log-logistic	45,210	1.01	44,692
2	Parametric extrapolation OS cut-off – 0 weeks log-logistic	43,814	0.89	49,407
3	Paclitaxel/nab-paclitaxel as for UK market shares	51,951	1.69	30,780
4	Utilities – progression based (pooled)	51,931	1.52	34,143
5	Utilities – time to death (per treatment arm)	51,931	1.58	32,784
6	Assuming treatment effect stops at three years	46,662	0.78	54,982
7	Assuming treatment effect stops at five years	45,478	1.54	40,027
8	Parametric extrapolation PFS – 26 weeks Gen-Gamma	51,931	1.61	32,170
9	Parametric extrapolation ToT – Exponential	52,633	1.69	31,144

Analysis provided for the overall population produced a similar result (ICER £29,769 with PAS). In the comparison versus pembrolizumab monotherapy in patients with TPS≥50%, pembrolizumab combination dominated monotherapy (i.e. was cheaper and more effective), though not when time on treatment was proxied by PFS.

There were a number of weaknesses associated with the analysis:

- The main weakness in the analysis concerns the estimation of long-term overall survival, due to the immaturity of the data cut employed in the analysis. Reliance on SEER data, though allowing an alternative baseline survival that might be considered more appropriate than one based purely on the immature KEYNOTE-407 data, is a limitation. The company applies a long-term treatment effect based on a relative risk estimated using data for months 7-12 in KEYNOTE-407. Though the RR estimate is in line with the overall HR reported in KEYNOTE-407, and the company cites evidence from KEYNOTE-010 for continued treatment benefit, there is inevitably some uncertainty over how long this should be applied given a) the short term nature of the data on which the estimate is based, and b) the planned duration of treatment (two years).
- Analyses limiting the treatment effect to a three to five year period had a notable impact on the ICER. Cost-effectiveness was also found to be sensitive to the choice of survival distribution coupled with short term Kaplan-Meier data when this approach was applied in place of the SEER based analysis, and for the submitting company's preferred parametric distribution, to the time point from which this was applied.
- The overall population analysis can be expected to be subject to the same limitations in terms of long-term survival and treatment effects as the TPS<50% analysis and the monotherapy indirect comparison did not provide evidence of survival benefit nor a significant treatment

effect on progression however as noted, a finding of dominance was reported in the cost-effectiveness analysis.

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 satisfied.

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 use in NHSScotland.

Additional information: guidelines and protocols

The European Society for Medical Oncology (EMSO) published a clinical practice guideline on the diagnosis, treatment and follow-up of metastatic NSCLC in 2018.[11] This guidance makes the following recommendations:

- The recommended therapy for Stage IV NSCLC patients with PD-L1 TPS ≥50% and an ECOG score of 0 or 1 is pembrolizumab monotherapy.

- Pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel is recommended as a standard choice in patients with metastatic squamous NSCLC. (This had not been EMA approved at the time of publication).

- Nivolumab plus ipilimumab is a treatment option for NSCLC patients with a high tumour mutational burden (This had not been EMA approved at the time of publication).

- Chemotherapy treatment with platinum doublets should be considered in all stage IV NSCLC patients without an actionable oncogenic driver, without major comorbidities and ECOG score of 0 to 2. This is the recommended option particularly in patients who have contraindications to immunotherapy.

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 137, Management of lung cancer in February 2014.[14] The guidance recommends that patients who have advanced squamous 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. This guideline predates the availability of pembrolizumab monotherapy for advanced NSCLC and the current treatment regimen of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel for metastatic squamous NSCLC.[14]

Additional information: comparators

PD-L1 TPS ≥50%: pembrolizumab monotherapy.
PD-L1 TPS <50%: chemotherapy containing either carboplatin or cisplatin, and one of the following: docetaxel, paclitaxel, etoposide, gemcitabine, or vinorelbine.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
Pembrolizumab, carboplatin, and paclitaxel(nab-paclitaxel)	**Pembrolizumab: 200mg via IV infusion every 3 weeks.** **Paclitaxel: 200mg/m^2 by IV infusion on Day 1 of each 21-day cycle for 4 cycles** **Carboplatin: AUC 6mg/ml/min by IV infusion on Day 1 of each 21-day cycle for 4 cycles.**	**Pembrolizumab/ carboplatin/ paclitaxel cycle: £6,197** **Pembrolizumab cycle: £5,260**
Pembrolizumab monotherapy	Pembrolizumab: 200mg via IV infusion every 3 weeks.	£5,260
Carboplatin and paclitaxel	Carboplatin: AUC 5mg/ml/min by IV infusion on Day 1 of each 21-day cycle for 4 cycles. Paclitaxel: 175mg/m^2 by IV infusion on Day 1 of each 21-day cycle for 4 cycles.	£826

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 07 May 2019. 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^2 and a glomerular filtration rate of 60ml/min was used for dose calculations, when applicable. Regimens are for illustrative purposes only; not all regimens have been included. IV= intravenous. AUC = area under the curve.

Additional information: budget impact

SMC is unable to publish the with- PAS budget impact or an estimate of patient numbers 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 14 June 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: 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.