Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2257

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

Merck Sharp and Dohme Limited

7 August 2020

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 accepted for restricted use within NHSScotland.

Indication under review: as monotherapy or in combination with platinum and fluorouracil chemotherapy, for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express programmed cell death ligand-1 (PD-L1) with a combined positive score (CPS)≥1.

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

Overall survival was longer in patients who received pembrolizumab as monotherapy or in combination with chemotherapy compared with a monoclonal antibody plus chemotherapy in a phase III study in patients with untreated, locally incurable, recurrent or metastatic HNSCC with PD-L1 CPS≥1.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ 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 as monotherapy or in combination with platinum and fluorouracil chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent HNSCC in adults whose tumours express PD-L1 with a CPS≥1.[1, 2]

Dosing Information

The recommended dose of pembrolizumab as monotherapy is either 200mg every 3 weeks or 400mg every 6 weeks administered as an intravenous infusion over 30 minutes.

The recommended dose of pembrolizumab as part of combination therapy is 200mg every 3 weeks administered as an intravenous infusion over 30 minutes. When administering pembrolizumab as part of a combination with intravenous chemotherapy, pembrolizumab should be administered first.

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.

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

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

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

Refer to the Summary of product characteristics (SPC) for further detail. [1, 2]

Product availability date

14 November 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 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.[3, 4]

Key evidence for this indication is from KEYNOTE-048, a multi-centre, randomised, open-label, phase III study. KEYNOTE-048 recruited adults with pathologically confirmed squamous cell carcinoma of the oropharynx, oral cavity, hypopharynx, or larynx that was recurrent or metastatic and not curable by local therapy. Eligible patients had not received prior systemic therapy in the recurrent or metastatic setting. Patients had at least one tumour lesion measurable per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 and had known human papillomavirus (HPV) status. Patients were also required to have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 and adequate organ function. Recruited patients provided a tumour sample for PD-L1 testing (PD-L1 positivity was not required for entry into the study).[3, 4]

Patients were randomised in a 1:1:1 ratio to receive open-label pembrolizumab alone, pembrolizumab in combination with chemotherapy, or cetuximab with chemotherapy. Randomisation was stratified according to the percentage of PD-L1-expressing tumour cells (≥50% or <50%), p16 status (HPV status) for oropharyngeal cancers (positive or negative; participants with non-oropharyngeal tumours were considered p16-negative), and ECOG performance status score (0 or 1). Pembrolizumab was given intravenously (IV) at a dose of 200mg every 3 weeks until disease progression, intolerable toxicity, physician or participant decision, or 35 cycles, whichever occurred first. The cetuximab dose was 400mg/m² IV loading dose, then 250mg/m² IV once a week until disease progression, intolerable toxicity, or physician or participant decision, whichever occurred first. The chemotherapy regimen consisted of IV carboplatin (area under the curve 5mg/mL/min) or IV cisplatin (100mg/m²) and IV fluorouracil (1000mg/m² per day for 4 consecutive days) every 3 weeks for six cycles. Investigators could switch patients from cisplatin to carboplatin during the study if toxicity occurred. If patients receiving cetuximab plus chemotherapy had to stop platinum and/or fluorouracil due to toxicity they could continue to receive cetuximab alone or in the event of cetuximab toxicity could continue on chemotherapy alone.[3, 4] Patients who had confirmed complete response and had received at least 24 weeks of treatment, including two doses of pembrolizumab beyond the first evidence of complete response, could discontinue pembrolizumab. Patients with unconfirmed disease progression who were clinically stable could continue on treatment at the discretion of the investigator until progression was confirmed with imaging carried out at least 28 days later.[3, 4]

The co-primary outcomes were overall survival, defined as the time from randomisation to death from any cause and progression-free survival (PFS), defined as the time from randomisation to radiographically confirmed disease progression (by blinded independent review committee) or death from any cause (whichever occurred first). Efficacy outcomes were evaluated for pembrolizumab alone versus cetuximab plus chemotherapy and for pembrolizumab plus chemotherapy versus cetuximab plus chemotherapy. The efficacy analyses were carried out in patients with PD-L1 CPS≥20, PD-L1 CPS≥1 and the full intention-to-treat population, defined as all patients randomly allocated to a treatment group.[3, 4]

Median follow up at the final analysis (data cut off 25 February 2019) was 11.5 months in the pembrolizumab monotherapy group, 13 months in the pembrolizumab with chemotherapy group and 10.7 months in the cetuximab plus chemotherapy group.

At the final analysis, pembrolizumab monotherapy and pembrolizumab plus chemotherapy were superior to cetuximab plus chemotherapy for overall survival in patients with PD-L1 CPS≥1 (indication under review). No PFS benefit was observed in the PD-L1 CPS≥1 population although this was not formally tested due to the hierarchical statistical plan.[3, 4] Secondary outcomes included the proportion of patients with objective response (defined as radiographically confirmed complete or partial response according to RECIST version 1.1) and the proportion of patients who were progression-free at 6 and 12 months. Duration of response was an exploratory outcome.[4, 5] Results are reported in table 1 for the PD-L1 CPS≥1 population, representative of the licensed indication.

Table 1: Primary and key secondary outcomes in KEYNOTE-048 for the PD-L1 CPS≥1 population at data cut off 25 February 2019.[3, 4]

	Pembrolizumab plus chemotherapy versus cetuximab plus chemotherapy		**Pembrolizumab monotherapy versus cetuximab plus chemotherapy**	
	Pembrolizumab plus chemotherapy (n=242)	Cetuximab plus chemotherapy (n=235)	Pembrolizumab monotherapy (n=257)	Cetuximab plus chemotherapy (n=255)
Overall survival				
Number of deaths	177	213	197	229
Median overall survival (months)	13.6	10.4	12.3	10.3
Hazard ratio (95% CI)	0.65 (0.53 to 0.8), p<0.001		0.74 (0.61 to 0.9), p=0.001	
KM estimate of overall survival at 12 months	55%	44%	50%	44%
KM estimate of overall survival at 24 months	31%	17%	29%	17%
PFS[a]				
Number of PFS events	212	221	228	237
Median PFS (months)	5.1	5.0	3.2	5.0
Hazard ratio (95% CI)	0.84 (0.69 to 1.02)		1.13 (0.94 to 1.36)	
KM estimate of PFS at 12 months	20%	12%	21%	14%
Secondary outcomes				
Objective response rate[b]	36%	36%	19%	35%
Complete response	6.6%	3.0%	5.4%	2.7%

Partial response	30%	33%	14%	32%
Median duration of response (months)	6.7	4.3	23.4	4.5

CI: confidence interval, KM: Kaplan-Meier, PFS: progression-free survival. [a]The final analysis for PFS was at interim analysis 2. [b]objective response rate defined as radiographically confirmed complete or partial response

Change from baseline in global health status/quality of life (QoL) to week 15, and time to deterioration in global health status/QoL, pain and swallowing were also included as secondary outcomes. The patient reported outcome population included all patients regardless of PD-L1 status who had at least one patient reported outcome assessment. Results showed similar baseline global health status/QoL scores between the pembrolizumab monotherapy or pembrolizumab plus chemotherapy groups and cetuximab plus chemotherapy groups with overall stable global health status/QoL from baseline to week 15. For the comparison between pembrolizumab monotherapy and cetuximab plus chemotherapy the Kaplan-Meier (KM) curves of time to deterioration for global health status and swallowing may indicate a detrimental effect, but the opposite trend was seen for pain. The KM curves of time to deterioration for global health status and pain may indicate a detrimental effect of pembrolizumab plus chemotherapy compared with cetuximab plus chemotherapy. [4]

The submitting company presented network meta-analyses (NMA) comparing pembrolizumab monotherapy and pembrolizumab with platinum (cisplatin or carboplatin) plus fluorouracil against platinum (cisplatin or carboplatin) plus fluorouracil. The outcomes included were overall survival and PFS. The networks formed for pembrolizumab monotherapy and combination therapy were similar for both outcomes, and fixed effect second order fractional polynomial models were used in all four analyses. Overall the results suggest that pembrolizumab monotherapy and combination therapy were associated with an improvement in overall survival and PFS compared with platinum chemotherapy plus fluorouracil. The NMA also included a comparison with cisplatin plus paclitaxel. No differences in overall survival were identified for the majority of time points except at 9 and 12 months for the pembrolizumab monotherapy comparison and 6 to 18 months for the pembrolizumab combination therapy comparison. However credible intervals were very wide. No PFS analysis was conducted for pembrolizumab monotherapy or combination therapy against cisplatin plus paclitaxel.

Summary of evidence on comparative safety

The European Medicines Agency (EMA) considered that for the first-line treatment of patients with metastatic or recurrent HNSCC, pembrolizumab plus chemotherapy had a similar safety profile to cetuximab plus chemotherapy. The safety profile appears consistent with the known safety profile of pembrolizumab and the chemotherapy medicines used. The EMA noted a higher incidence of serious adverse events in the pembrolizumab plus chemotherapy group however no individual serious adverse event raised particular concern. The EMA considered that pembrolizumab monotherapy had a favourable safety profile compared with cetuximab plus

chemotherapy, with the exception of hypothyroidism, which is expected taking into account the known toxicity of the chemotherapy regimen.[4]

In the safety population of KEYNOTE-048, the median duration of treatment was 3.5 months in the pembrolizumab monotherapy group, 5.8 months in the pembrolizumab plus chemotherapy group and 4.9 months in the cetuximab plus chemotherapy group. Adverse events thought to be related to treatment occurred in 58% (175/300) of the pembrolizumab monotherapy group, 96% (264/276) of the pembrolizumab plus chemotherapy group and 97% (278/287) of the cetuximab plus chemotherapy group. Treatment-related grade 3 or above adverse events were reported in 17% (51/300), 72% (198/276) and 69% (199/287) of the pembrolizumab monotherapy, pembrolizumab plus chemotherapy and cetuximab plus chemotherapy groups respectively. Adverse events leading to discontinuation of study treatment occurred in 12% (36/300), 33% (90/276) and 28% (79/287) of patients in the respective groups.[3]

Commonly reported adverse events of any grade in the pembrolizumab monotherapy, pembrolizumab plus chemotherapy and cetuximab plus chemotherapy groups included anaemia (21%, 58%, 47%), neutropenia (2%, 34%, 33%), thrombocytopenia (2%, 29%, 25%), hypothyroidism (18%, 16%, 6%), constipation (20%, 37%, 33%), diarrhoea (15%, 28%, 34%), nausea (16%, 51%, 51%), vomiting (11%, 33%, 28%), fatigue (28%, 34%, 36%), mucosal inflammation (4%, 31%, 28%), and decreased appetite (15%, 29%, 30%). Adverse events of interest attributed to pembrolizumab included hypothyroidism and pneumonitis.[3]

In the pembrolizumab monotherapy group three treatment-related deaths occurred; these were attributed to disseminated intravascular coagulation, autoinflammatory disease, and pneumonitis in one patient each. In the pembrolizumab plus chemotherapy group there were 11 treatment-related deaths. These were due to infections in seven patients (including five cases of septic shock) and tumour haemorrhage, cerebral ischaemia, interstitial lung disease, and haemorrhage in one patient each. There were 8 treatment-related deaths in the cetuximab plus chemotherapy group. Six of these were due to infections, one due to pulmonary artery thrombosis and one due to hypoxia.[4]

Summary of clinical effectiveness issues

Head and neck squamous cell carcinomas (HNSCC) are an anatomically heterogeneous group of cancers including tumours originating in the lip, oral cavity, hypopharynx, oropharynx, nasopharynx or larynx. Patients with metastatic or unresectable recurrent HNSCC have a poor prognosis and median overall survival is likely to be less than 1 year. Symptoms include pain and problems with speech, swallowing, and breathing. In Scotland patients may receive chemotherapy with platinum (cisplatin or carboplatin) and fluorouracil or paclitaxel. Some patients may receive alternative chemotherapy regimens, palliative radiotherapy or best supportive care.[4] Although cetuximab, in combination with platinum and fluorouracil, is licensed for this indication, it is not recommended for use by SMC due to non-submission (SMC number 547/09). Nivolumab is accepted for use within NHSScotland as monotherapy in patients progressing on or after platinum-

based therapy (SMC number 1261/17). Pembrolizumab is the first PD-1 inhibitor to be licensed for first-line treatment of metastatic or unresectable recurrent HNSCC. Clinical experts consulted by SMC considered that pembrolizumab fills an unmet need in this therapeutic area, namely improving overall survival. Pembrolizumab meets SMC end of life criteria.

KEYNOTE-048 demonstrated a significantly longer median overall survival for pembrolizumab as monotherapy or in combination with chemotherapy (platinum and fluorouracil) compared with cetuximab plus chemotherapy (platinum and fluorouracil) in patients with untreated locally incurable recurrent or metastatic HNSCC and PD-L1 CPS≥1. The improved overall survival results were not supported by PFS or objective response rate (ORR) results in either the pembrolizumab monotherapy or combination with chemotherapy comparisons with cetuximab plus chemotherapy. Conversely, in the pembrolizumab monotherapy comparison, PFS and ORR favoured cetuximab plus chemotherapy.[3, 4] The EMA considered that in patients whose disease expresses PD-L1 with CPS≥1, the balance/risk of pembrolizumab in combination with platinum and fluorouracil chemotherapy was favourable, since the survival benefits outweighed the risk in this population who have a dismal prognosis. The EMA considered an indication restricted to PD-L1 CPS≥1 patients was also acceptable for pembrolizumab monotherapy. In the PD-L1 CPS<1 population, no overall survival or PFS benefit was observed supporting the restriction of the licence to those with PD-L1 CPS≥1.[4]

KEYNOTE-048 did not include a comparison between pembrolizumab monotherapy and pembrolizumab in combination with chemotherapy. The EMA requested a descriptive comparison and noted that overall survival in both groups appeared similar.[4] At the final analysis, subsequent treatment had been received by almost half of patients. PD-1/PD-L1 inhibitors were received by more patients in the cetuximab plus chemotherapy group: 25% compared with 6% in each of the pembrolizumab groups.[3] Subsequent treatments could confound overall survival results. The EMA noted that in general sensitivity analyses performed to analyse the effect of switching identified similar overall survival results to the primary analyses.[4] The open-label design limits interpretation of patient reported QoL outcomes. Patients were required to have ECOG performance status score of 0 or 1 therefore study results may not be applicable to patients with a worse performance status. There are limited data in patients over 75 years, this has been noted in the SPC.[1, 2]

The comparator in the key study was cetuximab plus platinum chemotherapy and fluorouracil. Although cetuximab is licensed for this indication, it is not recommended for use by SMC due to non-submission. The comparators that are likely to be the most relevant for NHSScotland are platinum chemotherapy (carboplatin or cisplatin) and fluorouracil or paclitaxel. There are no direct data versus these comparators. The submitting company identified platinum and fluorouracil as the relevant comparator and presented NMAs to address the lack of direct data. The NMAs also included a comparison with cisplatin plus paclitaxel. The analyses had a number of limitations: the population was wider than the licensed indication (PD-L1 CPS≥1), there was heterogeneity in patient characteristics and study design, a number of treatments not relevant to current Scottish practice were included in the networks and much of the data was from studies that were published over a decade ago. Due to the nature of the networks formed, a random effects model could not be applied. Overall, despite the limitations, the results of the NMA suggest that

pembrolizumab monotherapy and combination therapy with platinum and fluorouracil were associated with an improvement in overall survival and PFS compared with platinum plus fluorouracil. The comparison with cisplatin plus paclitaxel is highly uncertain.

The introduction of pembrolizumab would provide an immunotherapy treatment option for first-line treatment of metastatic or unresectable recurrent HNSCC in adults whose tumours express PD-L1 with a CPS≥1. Expansion of PD-L1 testing may be required in NHSScotland therefore there may be service implications. Clinical experts consulted by SMC considered that pembrolizumab is a therapeutic advancement due to the associated survival benefit. They considered that the place in therapy would be as per the licensed indication. Pembrolizumab could be given in combination with chemotherapy or as monotherapy for patients not suitable for chemotherapy.

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 or unresectable recurrent HNSCC is a devastating condition with a poor prognosis. Patients have a life expectancy of 6 to 12 months. Symptoms can be severe including chronic pain, breathing difficulties, inability to speak and swallow as well as disfigurement of the face and neck. This can significantly impact patients' quality of life and can cause frustration, anger, depression and social withdrawal. Patients may feel they have lost their identity and often fear the unknown.

- There is significant unmet need in this patient group. The current treatment option for fit patients is platinum-based chemotherapy and median survival is less than 1 year. For patients expressing PDL1 CPS≥1 who receive pembrolizumab, with or without chemotherapy, a greater proportion are expected to be alive at 3 years than with current first-line treatment.

- Pembrolizumab would give patients the potential for improved disease control and a chance of survival beyond 2 years. Improving disease control could delay the worsening or improve symptoms and reduce the need for second-line treatments. This could improve quality of life and even allow some return to normal life which is very important to patients. There may be a longer duration of independent life and self-care which would reduce dependence on family/carers and support services. The introduction of pembrolizumab would give patients the opportunity to receive immunotherapy first-line, as many patients do not receive second line treatment and therefore are unable to receive immunotherapy at present.

- Administration of pembrolizumab is by a short infusion. For patients with disease suitable for pembrolizumab monotherapy, patients would avoid chemotherapy-related toxicity and spend less time in hospital receiving treatment. Pembrolizumab in combination with chemotherapy is likely to have little to no additional toxicity to chemotherapy alone.

Patient numbers will be small and unlikely to have a noticeable impact on oncology units and other services.

Additional Patient and Carer Involvement

We received a patient group submission from The Swallows, which is a registered charity. The Swallows have received 25% pharmaceutical company funding in the past two years, including from the submitting company. A representative from The Swallows participated in the PACE meeting. The key points of their submission 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 of pembrolizumab as monotherapy, and pembrolizumab in combination with platinum plus fluorouracil chemotherapy versus platinum plus fluorouracil chemotherapy, and versus cisplatin plus paclitaxel, for the first-line treatment of adult patients with metastatic or unresectable recurrent HNSCC whose tumours express PD-L1 with a CPS ≥1. SMC clinical expert feedback was that platinum plus fluorouracil chemotherapy is a relevant comparator. However, as noted above, cisplatin plus paclitaxel may also be a relevant comparator for the economic evaluation and the submitting company provided an additional analysis versus this comparator on request.

The economic analysis used a partitioned survival model with three health states (pre-progression, post-progression and death). The model used a weekly cycle with half cycle correction applied, and adopted a lifetime horizon of 20 years, with patients entering the model at a mean age of 61 years.

The clinical data for pembrolizumab were taken from the randomised, phase 3 KEYNOTE-048 study, which informed the patient baseline characteristics (age, gender, weight, body surface area), PFS and overall survival, treatment duration, utilities, and adverse events for the economic model.

As no relevant comparative data were available from the key study for pembrolizumab, indirect treatment comparisons (ITCs), consisting of network meta-analyses were performed to enable a comparison of PFS and overall survival outcomes for pembrolizumab monotherapy and pembrolizumab combination therapy versus platinum plus fluorouracil chemotherapy and versus cisplatin plus paclitaxel. Adverse events for the comparator were also sourced from the network meta-analyses or published literature.

The estimation of long-term overall survival outcomes used a piecewise extrapolation approach, applied from 80 weeks with the loglogistic function for pembrolizumab monotherapy and the lognormal function for pembrolizumab combination therapy. This predicted overall survival of 14% for pembrolizumab monotherapy and 19% for pembrolizumab combination therapy, at year 5. Progression-free survival was estimated over the long-term using a piecewise approach applied from 52 weeks with the exponential function used for both pembrolizumab monotherapy and

pembrolizumab combination therapy. Hazard ratios derived from the network meta-analyses were applied to pembrolizumab overall survival and PFS data to estimate outcomes for platinum plus fluorouracil and for cisplatin plus paclitaxel. No PFS data was available for cisplatin plus paclitaxel so this was assumed equivalent to platinum plus fluorouracil.

Time on treatment for pembrolizumab monotherapy and pembrolizumab combination therapy was based on KEYNOTE-048 data, with a stopping rule of 2 years applied. Treatment duration for platinum plus fluorouracil chemotherapy and cisplatin plus paclitaxel was assumed the same as PFS or a maximum of 6 cycles.

Utility values were derived using EQ-5D-3L data collected in the KEYNOTE-048 clinical trial using UK preference-based scores. The base case analysis used a mixed regression model to estimate utility values by health state and also accounted for time to death and grade ≥3 treatment-related adverse events for which utility decrements were applied. Utility values were age adjusted.

Costs included medicine acquisition, medicine administration, health state management, subsequent therapies, PD-L1 testing, treatment of adverse events, and terminal care. Resource use for routine follow-up care associated with health states were sourced from previous NICE health technology assessments.

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 NHS Scotland. Under the PAS, a discount was offered on the list price of pembrolizumab.

In the base case for pembrolizumab monotherapy versus platinum plus fluorouracil chemotherapy and pembrolizumab combination therapy versus platinum plus fluorouracil chemotherapy the incremental cost-effectiveness ratio (ICER) is estimated at £26,994 per quality adjusted life year (QALY) (Table 2) and £28,632/QALY gained (Table 3), respectively, with the PAS applied. Compared to platinum plus fluorouracil chemotherapy, pembrolizumab monotherapy was estimated to increase survival by 1.24 years and pembrolizumab combination therapy was estimated to increase survival by 2.02 years.

For the comparison with cisplatin plus paclitaxel, the base case ICER for pembrolizumab monotherapy is estimated at £33,830/QALY (Table 2) and for pembrolizumab combination therapy is £34,541/QALY gained (Table 3), with the PAS applied. Compared to cisplatin plus paclitaxel, pembrolizumab monotherapy was estimated to increase survival by 1.20 years and pembrolizumab combination therapy was estimated to increase survival by 1.90 years.

The main driver of cost differences is the medicine acquisition costs for both pembrolizumab monotherapy and pembrolizumab combination therapy, compared to the comparator.

Table 2: Base case results pembrolizumab monotherapy

Analysis	Treatment	Incremental costs	Incremental LYs	Incremental QALYs	ICER (cost/ QALY)
With PAS for pembrolizumab	Pembrolizumab monotherapy	£23,288	1.24	0.86	£26,994
	Platinum plus fluorouracil	-	-	-	-
With PAS for pembrolizumab	Pembrolizumab monotherapy	£28,539	1.20	0.84	£33,830
	Cisplatin + paclitaxel	-	-	-	-
ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; QALY, quality adjusted life year					

Table 3: Base case results pembrolizumab combination therapy

Analysis	Treatment	Inc. costs	Inc. Lys	Inc. QALYs	ICER (cost/ QALY)
With PAS for pembrolizumab	Pembrolizumab combination therapy	£39,787	2.02	1.38	£28,632
	Platinum plus fluorouracil	-	-	-	-
With PAS for pembrolizumab	Pembrolizumab combination therapy	£45,224	1.90	1.30	£34,541
	Cisplatin + paclitaxel	-	-	-	-
ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; QALY, quality adjusted life year					

In one-way sensitivity analysis the ICERs for pembrolizumab monotherapy and pembrolizumab combination therapy were most sensitive to variation in discount rates (outcomes and costs), overall survival parameters, starting age, and progressive disease utility value. A range of scenario analyses were performed, with the potentially most plausible scenarios presented in Tables 4 and 5 below. The scenario analyses which had the greatest upward impact on the ICER for pembrolizumab monotherapy and pembrolizumab combination therapy was alternative overall survival extrapolation for pembrolizumab, applying a reduced time horizon, and incorporating treatment waning.

Table 4: Selected scenario analysis results for pembrolizumab monotherapy at PAS price

Scenario analysis	Incremental cost	Incremental QALY	ICER (cost/QALY)
Pembrolizumab monotherapy versus platinum plus plus fluorouracil			
Time horizon (reduced to 10 years)	£21,878	0.64	£33,996
Pembrolizumab monotherapy OS: 80 weeks with lognormal distribution (alternative good statistical fit)	£23,819	0.96	£24,640

Pembrolizumab monotherapy OS: 80 weeks with Weibull distribution (conservative extrapolation)	£22,128	0.63	£35,026
Use mean utilities for health states (rather than utilities from the regression analysis)	£23,288	0.85	£27,404
Treatment waning - linear decline in benefit from 5 years	£21,899	0.58	£37,166
Treatment waning – equal to comparator at 5 years	£21,159	0.40	£52,602
Lower bound hazard ratios from the 95% CI for OS	£19,473	0.27	£71,877
Pembrolizumab monotherapy versus cisplatin + paclitaxel			
Time horizon (reduced to 10 years)	£27,277	0.64	£42,512
Pembrolizumab monotherapy OS: 80 weeks with Weibull distribution (conservative extrapolation)	£27,509	0.63	£43,228
Pembrolizumab monotherapy OS: full parametric with loglogistic (best statistical fit)	£28,059	0.74	£37,840
Use mean health state utilities	£28,539	0.83	£34,267
Treatment waning - linear decline in benefit from 5 years	£27,580	0.65	£42,196
Treatment waning - equal to comparator at 5 years	£26,609	0.42	£62,863
ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; QALY, quality adjusted life year; OS overall survival; CI, confidence interval			

Table 5: Selected scenario analysis results pembrolizumab combination therapy at PAS price

Scenario analysis	**Incremental cost**	**Incremental QALY**	**ICER (cost/QALY)**
Pembrolizumab combination therapy versus platinum plus fluorouracil			
Time horizon (reduced to 10 years)	£36,246	0.98	£37,013
Pembrolizumab combination therapy OS: 80 weeks with Weibull distribution (conservative extrapolation)	£37,313	1.05	£35,621
Pembrolizumab combination therapy OS: full parametric with loglogistic (best statistical fit)	£37,176	0.99	£37,401
Use mean utilities for health states (rather than utilities from the regression analysis)	£39,787	1.33	£29,894

Treatment waning - Linear decline in benefit from 5 years	£34,275	0.64	£53,040
Treatment waning – equal to comparator at 5 years	£34,114	0.56	£60,721
Pembrolizumab OS equal to comparator 10 years	£36,964	0.97	£37,809
Lower bound hazard ratios from the 95% CI for OS	£36,623	0.91	£40,026
Pembrolizumab combination therapy versus cisplatin + paclitaxel			
Time horizon (reduced to 10 years)	£41,841	0.91	£45,641
Pembrolizumab combination therapy: 80 weeks with Weibull distribution (conservative extrapolation)	£42,983	1.01	£42,417
Pembrolizumab combination therapy: full parametric with lognormal (best statistical fit)	£42,487	0.96	£43,877
Use mean health state utilities	£45,224	1.25	£36,053
Treatment waning - linear decline in benefit from 5 years	£41,832	0.84	£49,326
Treatment waning - equal to comparator at 5 years	£40,152	0.56	£71,283
ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; QALY, quality adjusted life year; OS overall survival; CI, confidence interval			

The economic analysis was associated with a number of weaknesses and uncertainties:

- There is a lack of head-to-head clinical evidence versus a relevant comparator for Scottish clinical practice in the main clinical evidence study KEYNOTE-048. Hence, indirect treatment comparisons were used to estimate the relative effectiveness of pembrolizumab (as monotherapy and as combination therapy with platinum plus fluorouracil) versus platinum plus fluorouracil. There are a number of limitations with the network meta-analyses performed, as noted in the summary of clinical effectiveness section above (e.g. NMAs being conducted in a wider population than the licensed indication, clinical and methodological heterogeneity and the possibility that a random effects model may have been more appropriate which would widen the credible intervals). Hence, there are uncertainties over the robustness of the relative treatment estimates used in the economic analyses.
- Uncertainty in the relative overall survival estimates on the ICERs when varying long-term extrapolation or when applying lower hazard ratios for overall survival for the treatment effect between pembrolizumab as monotherapy or as combination therapy, versus the comparators. Variations show upward sensitivity on the ICER.
- No treatment waning effect was considered for pembrolizumab when using relative effectiveness based on the NMAs. Scenario analyses showed upward sensitivity on the ICER

when incorporating treatment waning at 5 years assuming no additional benefit and also when assuming a declining benefit from 5 years.

The Committee also considered the benefits of pembrolizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission was satisfied, SMC can accept greater uncertainty in the economic case.

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

Additional information: guidelines and protocols

The 5th edition of the UK multidisciplinary guidelines for head and neck cancer were published in 2016.[5] The guidance is endorsed by the British Association of Endocrine and Thyroid Surgeons, British Association of Head and Neck Oncologists, British Association of Oral and Maxillofacial Surgeons, British Association of Otorhinolaryngology-Head and Neck Surgery, British Association of Plastic, Reconstructive and Aesthetic Surgeons, The Royal College of Pathologists and The Royal College of Radiologists (Faculty of Clinical Oncology). The guidance recommends that:

- concurrent chemoradiotherapy is at present the standard of care for treatment of locally advanced head and neck cancer
- chemotherapy or targeted biological agents may be indicated for patients with recurrent and/or metastatic disease
- targeted biological agents, such as cetuximab, have a role to play in both advanced head and neck cancer and recurrent or metastatic disease but those roles are still being established.[5]

The European Society for Medical Oncology (ESMO) published a clinical practice guidance on Squamous cell carcinoma of the head and neck in 2010.[6] This guidance was developed by the European Head and Neck Society (EHNS), the European Society for Radiotherapy and Oncology (ESTRO), and the ESMO guidelines working group. The guidance recommends that in instances of local, regional, and metastatic recurrence the "first-line option for fit patients should include the combination of cetuximab with cisplatin or carboplatin plus fluorouracil."[6]

SIGN90: diagnosis and management of head and neck cancer, published in 2006, was withdrawn in 2015.

Additional information: comparators

Carboplatin or cisplatin plus fluorouracil or paclitaxel.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Pembrolizumab	Monotherapy: 200mg intravenously every 3 weeks or 400mg every 6 weeks. Combination therapy: 200mg intravenously every 3 weeks.	89,420

Costs from BNF online on 30 January 2020. Costs do not take patient access schemes into consideration.

Additional information: budget impact

Pembrolizumab monotherapy
The submitting company estimated there would be 577 patients eligible for treatment with pembrolizumab monotherapy in year 1 and 583 in year 5, and accounting for treatment uptake and discontinuation estimates, resulted in 70 patients estimated to receive treatment in year 1 rising to 71 patients in year 5.

Pembrolizumab combination therapy
The submitting company estimated there would be 577 patients eligible for treatment with pembrolizumab combination therapy in year 1 and 583 in year 5, and accounting for treatment uptake and discontinuation estimates, resulted in 66 patients estimated to receive treatment in year 1 rising to 67 patients in year 5.

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

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

References

1. Merck Sharp & Dohme Limited. Pembrolizumab powder for concentrate for solution for infusion (Keytruda®). Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 25/11/19
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3. Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G, Jr., *et al.* Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019;31:31.
4. The European Medicines Agency (EMA) European Public Assessment Report. Pembrolizumab (Keytruda®). 17/10/2019, EMEA/H/C/003820/II/0065. www.ema.europa.eu.
5. Kelly CG. Chemotherapy: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130(S2):S71-S4. Epub 2016/11/15.
6. Gregoire V, Lefebvre JL, Licitra L, Felip E, Group E-E-EGW. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2010;21 Suppl 5:v184-6. Epub 2010/06/29.

This assessment is based on data submitted by the applicant company up to and including 12 March 2020.

**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.