SMC2688

pembrolizumab concentrate for solution for infusion (Keytruda®)

Merck Sharp & Dohme UK Limited

04 October 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

pembrolizumab (Keytruda®) is not recommended for use within NHSScotland.

Indication under review: in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults.

In a phase III, randomised, double-blind study, in patients with resectable, non-small cell lung carcinoma, the addition of neoadjuvant and adjuvant pembrolizumab to neoadjuvant chemotherapy significantly improved event-free survival and overall survival versus the addition of placebo.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Pembrolizumab is a humanised monoclonal antibody that blocks the interaction between programmed cell death-1 (PD-1) receptor and its ligands, PD-L1 and PD-L2. This potentiates T-cell responses, including antitumour responses of antigen presenting cells and tumours or other cells in the tumour microenvironment. For the neoadjuvant and adjuvant treatment of resectable non-small cell lung carcinoma (NSCLC), patients should be treated with neoadjuvant pembrolizumab in combination with chemotherapy for four doses of 200 mg every 3 weeks or two doses of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with pembrolizumab as monotherapy for 13 doses of 200 mg every 3 weeks or seven doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to pembrolizumab as neoadjuvant treatment in combination with chemotherapy should not receive pembrolizumab monotherapy as adjuvant treatment. See the Summary of Product Characteristics (SPC) for more details.[1]

1.2. Disease background

Lung cancer is the most common cancer in Scotland and in 2021 it accounted for 16% of all cancers. The most prevalent type is NSCLC, accounting for approximately 85% of all lung cancer cases. Most patients with lung cancer are diagnosed at an advanced stage. In Scotland in 2021, it was reported that 46% of lung cancer cases were diagnosed at stage IV, 20% at stage III and approximately 27% of patients were diagnosed at an early-stage (I or II).[2, 3]

1.3. Treatment pathway and relevant comparators

For patients who present with early NSCLC, stage I and II and selected IIIA, surgery with curative intent may be an option for suitable patients who are fit enough. Guidelines recommend adjuvant chemotherapy for patients with resected stage II and III NSCLC, taking account of performance status, comorbidities, time from surgery and recovery; for patients with stage IIA disease, adjuvant chemotherapy is recommended for those whose resected tumours were larger than 4 cm. The role of adjuvant chemotherapy in stage IB tumours is not clear and should be decided on individual basis and depending on the size of the tumour among other factors. For patients with resectable stage IIIA NSCLC who can have surgery and are fit enough for multimodality therapy, neoadjuvant chemoradiotherapy can be considered with surgery. Equivalence of neoadjuvant and adjuvant chemotherapy has been reported for overall survival.[3-6]

Recently, novel neoadjuvant and adjuvant treatments have been accepted for use in Scottish clinical practice for specific subgroups of early-stage resectable and resected NSCLC patients. These include nivolumab in combination with platinum-based chemotherapy for the neoadjuvant treatment of resectable NSCLC (SMC2619), adjuvant atezolizumab for stage II to IIIA NSCLC with PD-L1 expression on ≥50% of tumour cells (SMC2492) and adjuvant osimertinib for stage IB to IIIA epidermal growth factor receptor (EGFR) mutation-positive NSCLC (SMC2383). The most relevant comparator for this submission is nivolumab in combination with platinum-based chemotherapy for the neoadjuvant treatment of NSCLC.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of pembrolizumab in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment for the treatment of resectable NSCLC at high risk of recurrence, comes from KEYNOTE-671. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study[1, 3, 7]

Criteria	KEYNOTE-671
Study design	International, randomised, double-blind, phase III study.
Eligible patients	• Adults with previously untreated and pathologically confirmed resectable stage II, IIIA, or IIIB (N2) NSCLC assessed according to the AJCC staging system, 8th edition that was considered to be resectable after surgical consultation and investigator assessment. • Able to undergo protocol therapy, including necessary surgery. • ECOG performance status of 0 or 1. • Able to provide a tumour sample for PD-L1 assessment at central laboratory.
Treatments	Neoadjuvant pembrolizumab 200 mg IV on day 1 or placebo in combination with cisplatin 75 mg/m^2 BSA IV and either pemetrexed 500 mg/m^2 BSA IV (for patients with non-squamous tumours) on day 1 or gemcitabine 1,000 mg/m^2 BSA IV (for patients with squamous tumours) on days 1 and 8 of each 21-day cycle for up to four cycles. Following surgery (and in some cases radiotherapy), pembrolizumab 200 mg IV or placebo was given every 3 weeks for up to 13 cycles. Treatment was continued until completion of the treatment (17 cycles), disease progression that precluded definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection and entered the adjuvant phase, or unacceptable toxicity. The adjuvant phase was to be initiated no sooner than 4 weeks and no later than 12 weeks after surgery.
Randomisation	Participants were randomised equally to the pembrolizumab or placebo groups. Randomisation was stratified by stage (II versus III), tumour PD-L1 expression (TPS ≥50% or <50%), histology (squamous versus non-squamous) and geographic region (East Asia versus non-East Asia).
Primary outcome	The co-primary outcomes were: • EFS, defined as the time from randomisation to the first occurrence of local progression that precluded the planned surgery, unresectable tumour, progression or recurrence according to the RECIST version 1.1, as assessed by the investigator, or death from any cause. • OS, defined as the time from randomisation to death from any cause.
Secondary outcomes	• mPR, defined as ≤10% viable tumour cells in resected primary tumour and lymph nodes. • pCR, defined as the absence of residual invasive cancer in resected primary tumour and lymph nodes.
Statistical analysis	The overall type I error rate (for the four outcomes listed above) was controlled at a 2.5% one-sided significance level using the graphical method of Maurer and Bertz. This method tests individual hypotheses in a group

	sequential fashion using an error spending approach. Efficacy analyses were performed in the intention-to-treat population, which included all patients who underwent randomisation.

Abbreviations: AJCC = American Joint Committee on Cancer; BSA = body surface area; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; IV = intravenous; mPR = major pathological response; NSCLC = non-small cell lung carcinoma; OS = overall survival; pCR = pathological complete response; PD-L1 = programmed death-ligand 1; RECIST = Response Evaluation Criteria in Solid Tumours; TPS = tumour proportion score.

In patients with resectable, early-stage NSCLC, neoadjuvant pembrolizumab plus chemotherapy followed by resection and adjuvant pembrolizumab significantly improved event-free survival (EFS) and overall survival (OS) compared with the control arm. See Table 2.2 for details.

Table 2.2. Key efficacy outcomes from KEYNOTE-671 (ITT population; Interim analysis 2 data cut-off 10 July 2023).[3, 8]

	Pembrolizumab plus chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) (n=397)	**Placebo plus chemotherapy (neoadjuvant) followed by placebo (adjuvant) (n=400)**
Median follow-up	31.5 months	28.9 months
Co-primary outcome: event-free survival (investigator-assessed, RECIST v1.1 criteria)		
Events	174	248
Median EFS	47.2 months	18.3 months
Hazard ratio (95% CI)	0.59 (0.48 to 0.72) p<0.001*	
EFS rate at 12 months	74%	61%
Co-primary outcome: overall survival		
Events	110	144
Median OS	NR	52.4 months
Hazard ratio (95% CI)	0.72 (0.56 to 0.93) p=0.005	
OS rate at 24 months	79%	75%
Key secondary outcome: pathological complete response by BIPR		
Rate	18%	4.0%
Key secondary outcome: major pathological response by BIPR		
Rate	30%	11%

*EFS was not formally tested at interim analysis 2. This p-value is descriptive only. EFS at interim analysis 1 was statistically significant.

Abbreviations: BIPR = blinded independent pathological review; CI = confidence interval; EFS = event-free survival; ITT = intention-to-treat; NR = not reached; OS = overall survival; RECIST = Response Evaluation Criteria in Solid Tumours.

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life questionnaire (QLQ-C30) and lung cancer QLQ-LC13 questionnaires. These instruments were used at baseline, the last scheduled pre-

surgery visit, adjuvant cycles 1 to 4, 7, 10 and 13 and each post-treatment visit. There were no differences in least-squares mean change from baseline in the neoadjuvant or adjuvant phases for any patient-reported outcome score, suggesting the addition of perioperative pembrolizumab to neoadjuvant chemotherapy and surgery maintains quality of life.[9]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing pembrolizumab with relevant comparators, the submitting company presented an indirect treatment comparison. This has been used to inform the economic case. Details are presented in Table 2.3.

Table 2.3: Summary of indirect treatment comparison

<table>
<tr><th>Criteria</th><th>Overview</th></tr>
<tr><td>Design</td><td>Network meta-analysis (NMA).
Due to uncertainty regarding the proportional hazards assumption and if the hazard ratio would remain constant over time, the submitting company presented fixed and time-varying hazard ratio analyses.</td></tr>
<tr><td>Population</td><td>Adult patients with early-stage, resectable non-small cell lung cancer (NSCLC).</td></tr>
<tr><td>Comparators</td><td>Neoadjuvant nivolumab plus platinum-based chemotherapy, neoadjuvant platinum-based chemotherapy and active monitoring (surgery alone).</td></tr>
<tr><td>Studies included</td><td>Five studies (KEYNOTE-671[7, 8], CheckMate 816[10, 11], CHEST[12], Felip 2010[13] and Pisters 2010[14]).</td></tr>
<tr><td>Outcomes</td><td>Event-free survival.</td></tr>
<tr><td>Results</td><td>The fixed hazard ratio analysis, based on fixed effects, showed pembrolizumab improved EFS compared to surgery alone and neoadjuvant chemotherapy and had similar effects compared with the nivolumab regimen. In the time-varying hazard ratio analyses (fixed and random effects) comparing the pembrolizumab and nivolumab regimens, the point estimate at 3 months favoured nivolumab and the point estimates at 12 and 48 months favoured pembrolizumab. However, at all time points the 95% credible intervals (CrI) crossed 1.0, suggesting there may be no difference in EFS between treatments.
<table>
<tr><th>Analysis</th><th colspan="2">EFS HR (95% CrI)</th></tr>
<tr><td></td><td>Peri-adjuvant pembrolizumab versus surgery alone</td><td>Peri-adjuvant pembrolizumab versus neoadjuvant nivolumab</td></tr>
<tr><td colspan="3">Time-varying NMA</td></tr>
<tr><td>Fixed effects</td><td>3 months: 0.49 (0.33 to 0.71)
12 months: 0.48 (0.37 to 0.63)
48 months: 0.48 (0.32 to 0.70)</td><td>3 months: 1.30 (0.72 to 2.36)
12 months: 0.79 (0.53 to 1.18)
48 months: 0.61 (0.34 to 1.10)</td></tr>
<tr><td>Random effects</td><td>3 months: 0.47 (0.14 to 1.39)
12 months: 0.48 (0.14 to 1.37)
48 months: 0.48 (0.14 to 1.38)</td><td>3 months: 1.26 (0.31 to 4.60)
12 months: 0.79 (0.20 to 2.70)
48 months: 0.62 (0.15 to 2.19)</td></tr>
</table>
</td></tr>
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3. Summary of Safety Evidence

In the KEYNOTE-671 study at data cut-off 29 July 2022, the median duration of treatment was 291.5 days in the pembrolizumab group (n=396) and 271.9 days in the placebo group (n=396). In the pembrolizumab and placebo groups respectively, patients reported a grade 3 or higher adverse events (AE) were 65% versus 53%, patients with a reported serious AE were 40% versus 33% and patients discontinuing any drug due to an AE was 26% versus 17%.[3]

The most frequently reported treatment-related AEs of any grade with an incidence >10% in the pembrolizumab group versus the placebo group were: nausea (54% versus 51%), neutrophil count decreased (42% in both groups), anaemia (36% versus 34%), white blood cell count decreased (28% versus 25%), fatigue (27% versus 24%), constipation (27% versus 25%), decreased appetite (23% versus 22%), vomiting (19% versus 14%), platelet count decreased (19% versus 18%), blood creatinine increased (14% versus 12%), diarrhoea (13% versus 14%), alanine aminotransferase increased (13% versus 7.8%), asthenia (11% versus 14%), rash (11% versus 6.5%) and alopecia (10% in both groups).[3]

In KEYNOTE-671, the most frequently reported potentially immune-mediated AEs in the pembrolizumab group versus the placebo group were hypothyroidism (11% versus 1.8%), hyperthyroidism (5.6% versus 3.3%) and pneumonitis (5.6% versus 1.8%). Overall, the safety profile of pembrolizumab plus chemotherapy as neoadjuvant treatment, and then as monotherapy as adjuvant treatment, appeared to be consistent with the known safety profile of pembrolizumab and no new safety signals were identified.[1, 3]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- KEYNOTE-671 is a well-conducted, randomised, double-blind, phase III study.
- Pembrolizumab was associated with a statistically significant benefit in EFS; median EFS was 47.2 months in the pembrolizumab group versus 18.3 months in the placebo group; the estimated EFS rate at 12 months was 74% and 61% respectively. These results can be considered clinically meaningful.[3]
- At median follow-up 29.8 months, pembrolizumab was associated with a statistically significant benefit in OS; median OS not reached versus 52.4 months in the pembrolizumab and placebo groups respectively; HR 0.72 (95% CI: 0.56 to 0.93).[3]

4.2. Key uncertainties

- There was no direct evidence available comparing pembrolizumab with the most relevant comparator in this setting, nivolumab in combination with chemotherapy for the neoadjuvant treatment of NSCLC. The indirect treatment comparison (ITC) had several limitations meaning the results were highly uncertain. These included heterogeneity across the studies, comparison of different treatment settings, sparse data in the network, small sample sizes at later data points and that EFS was the only outcome considered.

- Overall survival data for KEYNOTE-671 are immature; 28% (110/397) and 36% (144/400) of patients in the pembrolizumab and placebo groups respectively had died at the latest data cut; median OS has not been reached in the pembrolizumab group. Further data are awaited.[3]
- There were a limited number of patients aged over 75 years in KEYNOTE-671 (7.2% of the total study population). As a result, the SPC recommends that pembrolizumab in combination with chemotherapy in this setting should be used with caution in patients aged over 75 years after careful consideration of the risks and benefits.[1, 3]
- KEYNOTE-671 only permitted neoadjuvant cisplatin-based regimens; carboplatin-based regimens were not permitted.[7]

4.3. Clinical expert input

Clinical experts consulted by SMC did not identify any unmet need.

4.4. Service implications

Compared with nivolumab in this setting, which is only used in the neoadjuvant phase and not in the adjuvant phase, pembrolizumab will likely require additional service resource for administration and monitoring.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- 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 organization.

- The Roy Castle Lung Cancer Foundation has received 7.6% pharmaceutical company funding in the past two years, including from the submitting company. The Scottish Lung Cancer Nurses Forum has not received any pharmaceutical company funding in the past two years.

- Living with lung cancer can be challenging with symptoms that are difficult to control e.g. breathlessness, continuous cough, and fatigue. Overall quality of life is impacted by not being able to do daily tasks, work, care for children and this can create an enormous stress on people with lung cancer and their loved ones.

- There are limited treatments for those who have a PD-L1 expression of below 50% post-surgery. Offering these patients further treatment could possibly have a huge impact on the emotional and mental health of both them and their loved ones.

- Many patients feel and do much better because they are having treatment, it is the hope with something active that is destroying the cancer cells, and they are often devastated if no treatment is offered. Pembrolizumab is already a commonly used treatment for lung cancer and potentially adds benefits for both patients and society in preventing or delaying

recurrence following surgery to resect their lung cancer.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The economic analysis is summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	36.9 years with a mean starting age of 63.1 years
Population	Patients with resectable non-small cell lung carcinoma at high risk of recurrence in adults
Comparators	The comparators in the model were: • Neoadjuvant chemotherapy • Neoadjuvant nivolumab in combination with chemotherapy • Surgery alone
Model description	A four-state Markov cohort model was used. The included states were event-free (EF), loco-regional recurrence/progression (LR/P), distant metastasis (DM) and death. All patients entered the model in the EF state before transitioning to subsequent states across the course of the model. No backward progression from more severe to less severe states was permitted.
Clinical data	The main source of clinical evidence for pembrolizumab and neoadjuvant chemotherapy was the KEYNOTE-671 study.[7] A random effects network meta-analysis was used to estimate the time-variant hazard ratios between peri-adjuvant pembrolizumab and the comparators of neoadjuvant nivolumab in combination with chemotherapy and surgery alone.
Extrapolation	From the EF state, patients could transition to the LR/P, DM and death states. For the transitions in the pembrolizumab and neoadjuvant chemotherapy arms independent generalised gamma functions were fitted to the KEYNOTE-671 study data to project transitions between the EF and LR/P and DM states. For the transitions from EF to death, a log-normal function was used. To model the transitions out of the EF state in the neoadjuvant nivolumab and surgery alone arms, the per cycle time-varying hazard ratios from the NMA were applied to the overall hazard of EFS in the pembrolizumab arm. The hazard ratios were applied directly until 5.2 years (which corresponded with the end of observed study data), after which the ratios was assumed constant. To estimate the destination of the transition, the company assumed that the proportions of the transitions from EF to the remaining states were the same for neoadjuvant nivolumab and surgery alone as they were in the pembrolizumab arm. The company implemented a cure rate, for patients remaining in the EF state, starting in year 5 and increasingly linearly until year 7, where 95% of patients were assumed to be no longer at risk of recurrence. KEYNOTE-671 did not collect data on patients after an event had taken place. Transitions from the LR/P state were estimated by applying exponential functions to data from patients with resectable NSCLC from the real-world SEER-Medicare database. These transitions were applied uniformly across the treatment arms. Transitions from the DM state were dependent upon the assumed first-line treatment for metastatic NSCLC. Overall survival at this stage was estimated from external sources. The company applied an adjustment factor which increased the DM mortality rate in the model, in an attempt to correct for meaningful differences between the modelled group and the patients in the clinical studies.

Quality of life	EQ-5D-5L data were collected as part of the KEYNOTE-671. These data were mapped to EQ-5D-3L using the mapping function developed by Alava et al. 2023[15] and valued using the UK value set. These data were used to estimate health state utility values for the EF state (0.830), the LR/P state (0.776) and the DM (pre-progression) sub-state (0.727). The company reported that there was insufficient data in the KEYNOTE-671 study to generate utility values in the DM (post-progression) state. The company combined utility estimated from the KEYNOTE-407[16] study for patients with squamous histology, utility values from KEYNOTE-189[17, 18] for patients with non-squamous histology and proportions of squamous vs non-squamous patients in the KEYNOTE-671 study (combined value of 0.669). A grade 3 or higher adverse event disutility was estimated from KEYNOTE-671 participants and combined with reported adverse event rates from the clinical studies to generate a one-off quality adjusted life year (QALY) loss in each arm.
Costs and resource use	Medicine costs included in the model were for acquisition costs (of three lines of treatment at the EF, LR/P and DM stage), administration costs and adverse events costs. The model included the costs of surgery and radiotherapy in the EF and LP/R states. Additionally, hospitalisation costs, outpatient visits, consultations with nurses, GPs and occupational therapists, monitoring (CT scans, chest radiography and ECG) and end of life costs were included.
PAS	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. Under the PAS, a discount was offered on the list price. A PAS discount is in place for nivolumab and this was included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence and competition law concerns regarding the PAS, SMC is unable to publish these results. The company considers all results confidential and so they are not presented here. Base case economic results suggested that treatment with pembrolizumab would result in higher total costs than when the comparator treatments are used. The main source of these increased costs was the higher treatment acquisition cost with pembrolizumab. However, the analysis also estimated that pembrolizumab treatment would be associated with better health outcomes through longer occupancy of the EF state.

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

6.3. Sensitivity analyses

To explore areas of uncertainty the company conducted deterministic sensitivity analysis and probabilistic sensitivity analysis. These analyses suggested that the main drivers of the economic results were the transition probabilities in the LR/P and DM states and the methodology used in estimating the hazard ratios for EFS between pembrolizumab, neoadjuvant nivolumab plus chemotherapy and surgery alone arms.

A selection of scenarios considered by the SMC Committee are presented in Table 6.3.

Table 6.3: Scenario analysis

	Parameter	Base case	Scenario	Neoadjuvant chemo	Neoadjuvant nivo + chemo	Surgery alone
1	Time horizon	36.9 years	20 years	**CIC**	**CIC**	**CIC**
2			30 years	**CIC**	**CIC**	**CIC**
3	Functions for modelling of transitions from EF state A: EF→LR/P, B: EF→DM, C: EF→death	A: Gen gamma B: Gen gamma C: Log-normal	A: Gen gamma B: Gen gamma C: Gen gamma	**CIC**	**CIC**	**CIC**
4			A: Gompertz B: Gen gamma C: Log-normal	**CIC**	**CIC**	**CIC**
5			A: Gen gamma B: Gompertz C: Log-normal	**CIC**	**CIC**	**CIC**
6	HRs used to model EF in nivolumab and surgery arms	Mean estimated HRs used to model nivolumab arm	Pembrolizumab and nivolumab assumed equivalent	**N/A**	**Requested, but the company declined to provide**	**N/A**
7		Time-variant HRs	Time-constant HRs	**CIC**	**CIC**	**CIC**
8	NMA model	Weibull random effects	Gompertz random effects	**CIC**	**CIC**	**CIC**
9	Dosing schedule for pembrolizumab	400 mg Q6W in adjuvant setting*	200 mg Q3W in adjuvant setting	**CIC**	**CIC**	**CIC**
10	pCR stopping rule (patients with a pCR do not receive adjuvant treatment with pembrolizumab)	No stopping rule	Stopping rule	**CIC**	**CIC**	**CIC**

Abbreviations: Gen gamma = Generalised gamma; chemo = chemotherapy, pembro = pembrolizumab; HR = hazard ratio; EF = Event-free; DM = distant metastasis; AEs = adverse events; QXW = every X weeks CIC = commercial in confidence

*Base case assumes that adjuvant pembrolizumab was administered as 1 cycle of 200 mg followed by a maximum of 6 cycles of a 400 mg dose every 6 weeks

6.4. Key strengths

- The model structure was appropriate and similar to those used in other SMC submissions for similar indications.
- Neoadjuvant nivolumab in combination with chemotherapy therapy is included in the list of comparators. Feedback from SMC clinicians suggested that this was the most relevant comparator in Scotland.

- The company's approach to fitting survival functions to the KEYNOTE-671 data, which estimated the transition probabilities from the EF state for peri-adjuvant pembrolizumab and neoadjuvant chemotherapy arms, appeared robust.
- Utility values for the majority of health states were estimated from the treatment population in the central study.

6.5. Key uncertainties

- KEYNOTE-671 compared pembrolizumab against chemotherapy. The wider range of relevant comparators necessitated the use of an NMA. Although the hazard ratios in the NMA favoured pembrolizumab over nivolumab, the wide credible intervals suggested no statistical difference in terms of EFS. In addition, the weaknesses in the NMA meant the results were considered highly uncertain. The economic modelling used the mean hazard ratio values in the base case, which led to a quality-of-life improvement for pembrolizumab patients over nivolumab patients. This was seen as uncertain, and while the company argued that this was an overly pessimistic interpretation of the evidence, the possibility that pembrolizumab was no more effective than nivolumab remained. If pembrolizumab and nivolumab had equal efficacy, pembrolizumab would lead to a positive net cost, with no health gain, due to the longer treatment time.

7. Conclusion

After considering all the available evidence, the Committee was unable to accept pembrolizumab for use in NHSScotland.

8. Guidelines and Protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published "Management of lung cancer: A national clinical guideline (SIGN 137)" in February 2014.[4]

The National Institute for Health and Care Excellence (NICE) published "Lung cancer: diagnosis and management" in 2019, which was updated in March 2024.[5]

The European Society for Medical Oncology (ESMO) published "Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" in 2017 and the guidance was subsequently updated in 2021.[6, 19]

9. Additional Information

9.1. Product availability date

09 May 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per course
pembrolizumab	**Neoadjuvant pembrolizumab in combination with chemotherapy for four doses of 200 mg every 3 weeks or two doses of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or**	**£94,680**

	unacceptable toxicity, followed by adjuvant treatment with pembrolizumab as monotherapy for 13 doses of 200 mg every 3 weeks or seven doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity.	

Costs from BNF online on 04 July 2024. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs assume nine doses of 400 mg as per the dose regimen. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 267 patients eligible for treatment with pembrolizumab in year 1, rising to 279 patients in year 5, to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the budget impact due to commercial in confidence issues.

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

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This assessment is based on data submitted by the applicant company up to and including 16 August 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.