Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2144

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

Merck Sharp & Dohme UK Ltd

5 April 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 considered under the orphan equivalent process

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

Indication under review: As monotherapy for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.

Recurrence-free survival was significantly longer in the pembrolizumab group compared with placebo in a phase III study of adult patients with completely resected, stage III melanoma with lymph node involvement.

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

As monotherapy for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.[1, 2]

Dosing Information

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

For the adjuvant treatment of melanoma, pembrolizumab should be administered until disease recurrence, unacceptable toxicity, or for a duration of up to one year.
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

December 2018

Pembrolizumab meets SMC orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor found in T-cells and blocks its interaction with ligands PD-L1 and PD-L2. This blockade potentiates T-cell responses resulting in immune-mediated anti-tumour activity.[1, 2] Pembrolizumab has previously been accepted by SMC for the treatment of unresectable or metastatic melanoma in patients previously untreated with ipilimumab (SMC 1086/15). For those patients who have been previously treated with ipilimumab, pembrolizumab is not recommended for use in Scotland (SMC 1087/15).

The evidence supporting this indication comes from KEYNOTE-054, an ongoing, randomised, double-blind, placebo-controlled phase III study. KEYNOTE-054 recruited adult patients with completely resected, histologically confirmed stage IIIA (with lymph-node metastasis >1mm), IIIB or IIIC cutaneous melanoma (according to the criteria of the American Joint Committee on Cancer, seventh edition). Complete regional lymphadenectomy had to be completed within 13 weeks of commencing treatment, and previous systemic therapy for melanoma was not permitted. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.[3]

Patients were randomised equally to receive intravenous (IV) pembrolizumab 200mg (n=514) or placebo (n=505) every three weeks, and were stratified according to disease stage (stage IIIA, IIIB, IIIC with one to three positive nodes, and IIIC with four or more positive nodes) and geographic location (17 regions). Study treatment was to continue for 18 doses (approximately one year) unless there was recurrence of disease, unacceptable toxicity, a major protocol violation or consent withdrawal.[3]

The primary outcome was recurrence free survival (RFS), defined as the time from randomisation until the date of first recurrence (local, regional, or distant metastasis) or death from any cause. RFS was assessed in all randomised patients, with data censored for patients lost to follow-up and those who were alive without evidence of disease progression at the end of the study.[3]

The primary outcome was analysed as part of a pre-specified interim analysis after 351 RFS events had occurred. At a median follow-up of 15 months, pembrolizumab was associated with a significant improvement in RFS compared with placebo in the intention-to-treat (ITT) population: 1-year rate of RFS, 75 % versus 61%; hazard ratio (HR) for recurrence or death, 0.57 (98.4% confidence interval (CI): 0.43 to 0.74; p<0.001). At 18 months, RFS was 71% in the pembrolizumab group and 53% in the placebo group. Analysis is not available beyond the 18 month mark due to limited patient numbers.[3] Further analysis indicated that pembrolizumab had similar levels of efficacy for the PD-L1 positive subgroup, RFS HR 0.54 (95% CI: 0.42 to 0.69).

Distant metastases-free survival (DMFS) and overall survival were secondary outcomes in the KEYNOTE-054 study but data are immature.

There were no clinically significant changes from baseline in quality of life in either treatment group as assessed with the European Organisation for Research and Treatment of Cancer (EORTC) quality of life 30 item questionnaire (QLQ-C30) and European Quality of Life 5 Dimension (EQ-5D) tools.[4]

Summary of evidence on comparative safety

At least one adverse event was reported in 93% (475/509) of patients in the pembrolizumab group compared with 90% (453/502) of patients in the placebo group of KEYNOTE-054. Of these reported AEs, 32% (161/509) and 18% (93/502) were greater than or equal to grade 3 in severity in the pembrolizumab and placebo groups respectively. Adverse events leading to permanent discontinuation of the study drug occurred in 14% (70/509) and 2% (11/502) of patients in the respective groups.[3]

The most common treatment-related AEs reported in the pembrolizumab (n=509) and placebo (n=502) groups were: fatigue or asthenia (37% versus 33%); skin reactions (28% versus 18%); diarrhoea (19% versus 17%); hypothyroidism (14% versus 3%); arthralgia (12% versus 11%); and nausea (11% versus 9%). Immune-related AEs of any kind occurred more often in the

pembrolizumab group compared with placebo (37% versus 9%), with colitis and pneumonitis being the most commonly reported treatment related serious adverse events. The overall safety profile was consistent with that established across tumour types for pembrolizumab monotherapy.[1, 2]

Summary of clinical effectiveness issues

Cutaneous melanoma is the fifth and sixth most common type of cancer in females and males respectively in Scotland, and the incidence is rising.[5] Ultra violet (UV) light exposure (both natural and artificial sunlight) is considered to be the main risk factor for cutaneous melanoma. It has a relatively young age distribution and often affects people of working age. About 90% of melanoma cases are diagnosed as primary tumours, with no evidence of metastasis.[6] These cases can be cured if recognised and treated with surgery at an early stage. However, for patients with advanced melanoma, prognosis is poor, with 5-year survival rates ranging between 40% and 80%.[5, 7] Recurrence rates remain high for these patients with local or distant metastasis, despite surgical intervention.[8] Treatment options are very limited for patients with stage III melanoma. Interferon alfa is licensed in Scotland for the treatment of resected melanoma in the adjuvant setting, but is not recommended for this use by the Scottish Intercollegiate Guidelines Network (SIGN) other than in a trial setting. In patients who undergo complete resection there is no standard adjuvant treatment in current practice and most patients are managed through routine surveillance.[5]

Clinical experts consulted by SMC considered that pembrolizumab fills an unmet need in this therapeutic area as these patients are at a high risk of recurrence and until recently there has been no adjuvant therapy available for this indication. Pembrolizumab meets SMC orphan equivalent criteria. Nivolumab has recently been accepted by SMC for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

In the pivotal KEYNOTE-054 study, pembrolizumab significantly improved RFS at one year compared with placebo (75% versus 61%). The study is ongoing and secondary outcome data for DMFS and overall survival are awaited.[3]

Median follow-up of patients in the KEYNOTE-054 study was 15 months, which is relatively short for this indication; median RFS had not been reached in either treatment group.[3] RFS is a surrogate outcome believed to be an effective predictor of overall survival. The EMA accepts that RFS is a valid outcome in melanoma studies but notes that overall survival should also be reported as adjuvant treatment may limit subsequent treatment options.[9] Overall survival data for pembrolizumab are currently immature.

Patients were required to have an ECOG status of 0 or 1 therefore it is unclear whether the results would apply to patients with a poorer performance status (≥2). Additionally, patients with stage IIIA disease were excluded if the lymph node metastases were <1mm. Therefore, patients with potentially better prognosis were excluded from the study. The licensed indication includes all

patients with stage III disease. It is not clear if the risk/benefit ratio is favourable for this subgroup of patients.

Patients with completely resected Stage IIIB or IIIC melanoma may be considered for adjuvant radiotherapy, though experts have not suggested that this would be considered routine practice in Scotland. Participants in the KEYNOTE-054 study were prohibited from any anti-cancer treatments during the study period, including radiotherapy

The KEYNOTE-054 study compared pembrolizumab with placebo, which can be considered a proxy for routine surveillance, the most relevant comparator. The impact of the use of pembrolizumab as adjuvant therapy on subsequent treatment in the metastatic setting is unknown. The best treatment sequencing is also unknown.

Clinical experts consulted by SMC considered that pembrolizumab is a therapeutic advancement due to significantly reducing the risk of relapse in this patient group. They considered that the place in therapy is adjuvant treatment of adult patients with Stage III melanoma following complete resection. Moreover, the clinical experts consulted by SMC considered that the introduction of this medicine may impact on the patient and/or service delivery as treatment for 12 months would have implications for the chemotherapy day unit. Additional oncology clinic capacity for on treatment reviews and follow-up on completion of treatment will also be required. Overall patient numbers for this indication will be small.

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 orphan-equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Stage III melanoma is associated with a high risk of recurrence. Generally, it affects younger patients compared with other cancers. This has an impact on the whole family; patients may be in work, parents, or carers for other family members.
- Before the introduction of immunotherapy treatments and targeted therapies for this indication, patients did not receive any treatment, and would be managed with routine surveillance. There is a high unmet need for treatments that reduce the risk of recurrence and increase the chance of a cure.
- By reducing the risk of recurrence, pembrolizumab may allow patients to function normally, work, and be independent for longer. In addition to benefitting the patient both mentally and physically, this would have a positive impact on family members by reducing the burden of care.
- Preventing progression to advanced melanoma is of the utmost importance for patients, as advanced melanoma is associated with greater symptom burden, poorer prognosis, and more intense treatment.

- Pembrolizumab has a 3 weekly administration schedule, which may be preferred by patients over an alternative treatment option.

Additional Patient and Carer Involvement
We received a patient group submission from Melanoma Action and Support Scotland (MASScot), which is a Scottish Charitable Incorporated Organisation (SCIO). MASScot has received 2.3% pharmaceutical company funding in the past two years, with none from the submitting company. A representative from MASScot 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 company submitted a cost-utility analysis which compared pembrolizumab against routine surveillance in the licenced indication. Routine surveillance was also described as 'watchful waiting' by the submitting company and medicines were not included within the comparator arm.

A Markov cohort model with a time horizon of 46 years was used to assess the cost-effectiveness of pembrolizumab versus routine surveillance. The model included four health states, recurrence-free (RF), loco-regional recurrence (LRR), distant metastases (DM), and death. Including LRR and DM health states allowed the model to differentiate by type of recurrence, with health outcomes and costs expected to be different for each recurrence type. All patients entered the model in the RF health state and patients could transition to a worse health state or die in the analysis. The economic model assumed that pembrolizumab would be continued for a maximum of 12 months.

Clinical data used in the model primarily included the KEYNOTE-054 study supplemented with registry data, KEYNOTE-006 and a NMA referenced by the company. The KEYNOTE-054 study data were used to estimate transitions from the RF health state for both pembrolizumab and RS; with data for placebo acting as a proxy for RS in the model. When modelling the risk of each event (i.e. LRR, DM or death) the company extrapolated the observed data over the duration of the time horizon using parametric functions and accounting for competing risks. In the base case analysis the Gompertz and generalised gamma functions were used to model transitions from RF to LRR and RF to DM respectively, and an exponential function for RF to death.

Transitions from the LRR health state were based on registry data (for LRR to DM) and KEYNOTE-054 (for LRR to death). The only transition patients could make in the DM health state was DM to death. DM transition probabilities were derived by modelling the efficacy of a range of treatments patients could receive in clinical practice at this stage of the disease pathway (using data from KEYNOTE-006 and a NMA). The analysis then combined the efficacy of these treatments using weighted averages to determine the final transition probability for the model.

Utility values for RFS, LRR, and DM (pre- progression) were derived from the EQ-5D-3L data collected in KEYNOTE-054. The values were 0.870, 0.830 and 0.775 respectively. A DM (post progression) utility of 0.581 was taken from a published study. The economic model also included disutilities for adverse events.

Medicine acquisition and administration costs for pembrolizumab were included in the analysis. Costs associated with salvage surgery, subsequent treatment, monitoring and management, best supportive care, adverse events, and terminal care were also included for both pembrolizumab and RS. It is worth noting in the DM health state patients could receive first and second line subsequent therapies and potentially switch to best supportive care.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price for pembrolizumab.

The base case results and selected sensitivity analyses for pembrolizumab versus RS with the PAS for pembrolizumab are shown in tables 1 and 2.

Table 1: Base case results (with PAS)

Comparator	**Incremental costs**	**Incremental QALYs**	**Incremental Life years**	**ICER**
Routine surveillance	-£64,239	2.68	3.21	Dominant*

QALY = quality-adjusted life-year, ICER = incremental cost-effectiveness ratio

*Pembrolizumab estimated to be more effective and less costly

Table 2: Selected Sensitivity Analysis

	Analysis	**ICER**
1	Time horizon: 10 years	Dominant
2	Distribution used for RF→LR and RF→DM: Log-logistic and Log-normal	Dominant
3	Include costs of first-line advanced regimens only	Dominant
4	Assume same mix of advanced treatments following adjuvant pembrolizumab and watchful waiting	Dominant
5	Utility in RF state - 10%	Dominant
6	Utility in post-progression DM +10%	Dominant
7	Transition probabilities from RF health state equal for pembrolizumab and routine surveillance from year 1 onwards	Dominant
8	Pembrolizumab RF->DM transition probabilities set equal to routine surveillance	Dominant
9	Transition probabilities from RF health state equal for pembrolizumab and routine surveillance from 18 months onwards in combination with the same mix of treatments in DM for both arms	£36,116

RF = recurrence-free, LR = locoregional recurrence, DM = distant metastases, ICER = incremental cost-effectiveness ratio

The main weaknesses were:

- There were limitations with the clinical data used to support the economic evaluation. For example, the median follow-up time for RFS from KEYNOTE-054 was only 15 months (with an economic model time horizon of 46 years) while the minimum number of events was not reached for DMFS and overall survival. Therefore, it was unclear if robust clinical data were available to support the transition probabilities used in the model. In addition, weaknesses with the supporting data created uncertainty in relation to the modelled benefits of pembrolizumab such as the magnitude of the extended duration recurrence-free, reduced time spent with distant metastases, and an incremental life year gain of 3.21 years (which is driven by differences in modelled RFS). SMC had concerns regarding the face validity of the dominance findings and thus it was helpful to have the more conservative model assumptions. The company subsequently provided sensitivity analysis where transition probabilities for pembrolizumab from year 1 (when patients have discontinued pembrolizumab) are the same as the RS arm of the model (Table 2 analysis 7; QALY gain reduced to 0.43, savings reduced to £34k). The company also provided a sensitivity analysis where the pembrolizumab transition probability for RF to DM was the same as RS thereby removing the benefit of pembrolizumab in terms of transitions from RF to DM (table 2 analysis 8; QALY gain reduced to 0.03, savings reduced to £26k).
- The economic model places a degree of focus on the treatments patients may receive if they develop DM and adopted a relatively complex approach to modelling the efficacy of these treatments alongside a detailed costing of subsequent therapies. In addition, it is the subsequent therapies patients received in DM which generates the "cost saving" result for pembrolizumab, as patients spend less time in the expensive DM health state. However, the impact of introducing pembrolizumab in the adjuvant setting on the efficacy of subsequent treatments and optimal treatment sequencing is an unknown. Also, many of the subsequent therapies have a PAS and these were not included in the base case economic model and any subsequent savings would therefore be overestimated. The company subsequently provided a sensitivity analysis where the same mix of treatments in the DM health state for pembrolizumab and routine surveillance are assumed, and the results are available in table 2 above (analysis 4; savings of £15k, QALY gain 2.79).
- In relation to the two bullet points above, the company provided a scenario which assumed the pembrolizumab RF to DM transition probabilities were equal to routine surveillance from 18 months onwards, and used the same mix of treatments in DM for both arms. As noted in table 2, this analysis generated an ICER of £36,116 (table 2 analysis 9) and demonstrates the importance of the assumptions around DM in influencing the results. The scenario analysis highlights the uncertainty in the model with the estimated longer term benefit with pembrolizumab given the immaturity of the data and that the treatment pathway for subsequent therapies is unknown and therefore it may be more appropriate to apply the same modelling assumptions to the DM health state in both arms.

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 pembrolizumab is an orphan-equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and 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 most up to date published guidelines for the assessment and management of melanoma of the skin includes:

- The Scottish Intercollegiate Guidelines Network (SIGN) 'Clinical Guidelines for Cutaneous Melanoma' (SIGN 146, 2017)[5]
- The European Society for Medical Oncology (ESMO) 'Cutaneous Melanoma Clinical Practice Guidelines' (2015) which was subsequently updated in September 2016[11]
- The National Institute for Health and Care Excellence (NICE) NG14 guideline 'Melanoma: assessment and management' (2015)[12]
- A collaboration between the European Dermatology Forum, the European Association of Dermato-Oncology and the European Organisation for Research and Treatment of Cancer 'Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline e Update 2016'.[6]

All these publications predate the availability of pembrolizumab as adjuvant treatment for resected stage III melanoma, and none provide recommendations on its use for this indication.

Additional information: comparators

There are no comparator treatments for this indication.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
Pembrolizumab	**200mg administered by intravenous infusion every 3 weeks, for up to a maximum of 12 months.**	**£94,680**

Costs from BNF online on 05 December 2018. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The company estimated there would be 132 patients eligible for treatment in year 1 rising to 146 in years 5 to which confidential uptake rates were applied.

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

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

References

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12. NICE. NG14 Melanoma: assessment and management. 2015 [cited; Available from: https://www.nice.org.uk/guidance/ng14.

This assessment is based on data submitted by the applicant company up to and including 15 February 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.