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Advising on new medicines for Scotland
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NHS SCOTLAND
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pembrolizumab (Keytruda®) 50mg powder for concentrate for solution for infusion and 25mg/mL concentrate for solution for infusion SMC No 1296/18

Merck Sharp and Dohme Ltd

9 February 2018

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the ultra-orphan and end of life process

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

Indication under review: As monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant and brentuximab vedotin, or who are transplant-ineligible and have failed brentuximab vedotin.

SMC restriction: treatment with pembrolizumab is subject to a two-year clinical stopping rule.
In a phase II study, pembrolizumab was associated with a clinically meaningful overall response rate in adults with classical Hodgkin lymphoma who had failed autologous stem cell transplant and brentuximab vedotin, or who were transplant-ineligible and had failed brentuximab vedotin.

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 NHS Scotland or a list price that is equivalent or lower.

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

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant and brentuximab vedotin, or who are transplant-ineligible and have failed brentuximab vedotin.[1]

Dosing Information

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

Treatment with pembrolizumab should be continued until disease progression or unacceptable toxicity. Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Please refer to the summary of product characteristics for advice on treatment modification for adverse events.

Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.[1]

Product availability date

2 May 2017

Pembrolizumab meets SMC ultra-orphan and end-of-life criteria in this indication.

Background

Pembrolizumab is a humanised monoclonal antibody which blocks the interaction between programmed cell death-1 (PD-1) receptor and its ligands PD-L1 and PD-L2. This results in the functional activity of the target lymphocytes being enhanced to facilitate immune-mediated anti-tumour activity. Pembrolizumab is the second PD-1 inhibitor (after nivolumab) to be licensed for treatment of adults with relapsed or refractory Hodgkin lymphoma who have failed brentuximab vedotin and failed previous autologous stem cell transplant (ASCT). It is the first PD-1 inhibitor to be licensed for treatment of adults with relapsed or refractory Hodgkin lymphoma who have failed brentuximab vedotin and were ineligible for ASCT.[1] It meets SMC end-of-life and ultra-orphan criteria.

Pembrolizumab for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

Hodgkin lymphoma is a lymphoid malignancy characterised by the presence of multinucleated Reed-Sternberg cells in the context of a mixed inflammatory background, which comprises lymphocytes (T-cells are usually predominant), eosinophils, neutrophils, macrophages, plasma cells and fibroblasts. The majority of cells in the tumour tissue are a mixed infiltrate of various lymphoid cells, including effector and regulatory T-cells and macrophage. Classical Hodgkin lymphoma accounts for about 95% of cases of Hodgkin lymphoma.[2]

A patient and clinician engagement (PACE) meeting was held to consider the added value of pembrolizumab in the context of treatments currently available in NHS Scotland. At the PACE meeting attention was drawn to the typically incurable prognosis for Hodgkin lymphoma after a patient has relapsed or is refractory to brentuximab vedotin given after failure of ASCT or to patients who are ASCT-ineligible. The poor prognosis and lack of effective treatment options can have a psychological impact on patients, many of whom are young adults, and their family and carers. The disease can also be associated with progressive debilitating physical symptoms, such as B symptoms (fever, night sweats and weight loss), fatigue and itch.

Impact of new technology

Summary of evidence on comparative efficacy

An open-label phase II study (KEYNOTE-087) recruited three cohorts of patients who:

- had failed to respond to or progressed after ASCT and failed to respond to or relapsed after brentuximab vedotin; or
- had failed to achieve at least a partial response with salvage chemotherapy and were therefore not suitable for ASCT and subsequently failed to respond to or relapsed after brentuximab vedotin; or
- had failed to respond to or progressed after ASCT and had subsequently not received brentuximab vedotin (although they may have received brentuximab vedotin as part of previous primary or salvage therapy). This cohort of patients is not representative of the licensed indication and is not discussed further.

Patients had measurable disease and a score of zero or one on the Eastern Cooperative Oncology Group (ECOG) performance status scale. All patients received open-label pembrolizumab 200mg intravenous (IV) infusion every three weeks for up to 24 months or until confirmed disease progression or unacceptable toxicity. If patients had progressive disease but a stable clinical condition at the week 12 assessment, they could continue treatment at the investigator's discretion until next response assessment. If patients had progressive disease after the week 12 assessment, treatment was discontinued. Patients achieving complete remission could discontinue treatment after a minimum of at least six months and two doses after complete response. If these patients later experienced progressive disease they were eligible, at the investigator's discretion, for re-treatment with pembrolizumab if they has not received cancer therapy since the last dose of pembrolizumab.

The primary outcomes were safety and objective response rate (ORR), defined as complete remission or partial remission on the International Working Group (IWG) revised response criteria (RRC) for malignant lymphoma and assessed by a blinded independent review committee (BIRC). Both outcomes were assessed in all patients who received at least one dose of study drug. ORR was compared with a fixed historical control rate of 20%.[1-3]

The study is ongoing. Currently, there have been three analyses. The first data cut-off was June 2016 after median follow-up of 7.1 months (range 1.0 to 12.1) when all patients had been followed-up for at least 12 weeks (i.e. first disease assessment).[2] The second data cut-off was September 2016 after a median follow-up of 10.1 months (range 1.0 to 15.0). It was the most up-to-date analysis submitted for the EMA review and was included in the summary of product characteristics (SPC).[1,2,5] The third data cut-off was March 2017 Data from this data cut-off were provided in confidence in this submission to support the economic analysis.[6]

The primary outcome, ORR, in each cohort was significantly greater than the historical control rate of 20%. Cohorts 1 and 2 are representative of the patients included in the licensed indication and results from these are detailed in table 1.

Table 1: Response rates in KEYNOTE-087

Data cut-off	Median follow-up	Overall response		Complete remission		Partial Remission	
		Cohort 1	Cohort 2	Cohort 1	Cohort 2	Cohort 1	Cohort 2
June 2016[2]	7.1 months	72% (50/69)	65% (53/81)	22% (15/69)	22% (18/81)	51% (35/69)	43% (35/81)
September 2016[2,3]	10.1 months	74% (51/69)	64% (52/81)	22% (15/69)	25% (20/81)	52% (36/69)	40% (32/81)

Median time to response at the first analysis (June 2016) was 2.7 and 2.8 months, in cohorts 1 and 2, respectively and may be reflective of the time of first disease assessment at 12 weeks.

In analyses at the data cut-off in June 2016 in patients who received at least one dose of study medication and completed at least one questionnaire, mean improvement from baseline to week 12 in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QOL-C30) global health status score was 8.5 points, with a mean change of 5.0 points in those who had progressive disease. In the European Quality of Life Five Dimensions Questionnaire (EQ-5D) visual analogue score, there were mean changes from baseline to week 12 of 10.7 and 5.2 points in those who had complete or partial response and stable disease respectively. QoL data from the September 2016 cut off were provided in confidence to SMC to support the economic analysis

KEYNOTE-013 is a single arm, phase Ib study of patients with haematological malignancies, and relevant data were available from a subgroup of 31 adults with relapsed or refractory nodular sclerosing or mixed cellularity classical Hodgkin lymphoma who had failed; were ineligible for; or refused a stem cell transplant. They had an ECOG performance status score of zero or one, measurable disease and had relapsed after or failed to respond to brentuximab vedotin. The primary outcome of complete response, based on IWG RRC, was assessed in the full analysis population, which comprised all patients who received at least one dose of study medication and had a baseline and at least one post-baseline efficacy evaluation or had discontinued due to adverse event or progressive disease. All patients received pembrolizumab 10mg/kg IV every two weeks (unlicensed regimen) until disease progression, unacceptable toxicity or a maximum of 52 doses (i.e. two years). At the data cut-off on 3 June 2016, after a median follow-up of 24.9 months (range 7.0 to 29.7 months), three patients remained on treatment, five patients had completed treatment and 23 had discontinued, with the majority due to progressive disease (n=14). The complete response rate by BIRC and site review was 19.4% (3/31) and the ORR, defined as complete or partial response, was 58% (18/31) by BIRC and 64% (20/31) by site review. Median time to response was 2.8 months and median duration of response was not reached (0+ to 21.4+).[2]

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

Summary of evidence on comparative safety

There were no comparative data available from the single-arm studies (KEYNOTE-087 and KEYNOTE-013) to support this new indication for pembrolizumab. The European Medicines Agency (EMA) review noted that overall the safety profile of pembrolizumab in Hodgkin Lymphoma was generally in line with that reported in melanoma and non-small cell lung cancer. However, a new safety concern identified was a potential increased risk of severe complications after allogeneic stem cell transplant (alloSCT) in patients previously given pembrolizumab. Overall, 23 patients treated with pembrolizumab (10 in KEYNOTE-087 and 13 in KEYNOTE-013) subsequently received an alloSCT. Complications were experienced by seven patients with two drug-related serious adverse events of veno-occlusive disease, one of which was fatal, and six reports of graft-versus-host disease, including one fatal case. Data on the feasibility of alloSCT after pembrolizumab are still limited. However, with consideration of pembrolizumab's immunomodulatory mechanism and the prolonged clinical activity possibly enhancing allogeneic T-cell responses, an increased risk of severe complications of alloSCT was regarded by the EMA as a new safety concern considered to be an important potential risk of pembrolizumab.[2]

Summary of clinical effectiveness issues

Clinical guidelines note that initial treatment of Hodgkin lymphoma usually consists of combined modality approaches (e.g. chemo- and radiotherapy) or chemotherapy alone, with intensity guided by the patient's risk profile. For patients with recurrence after first-line therapy, the standard of care is high-dose chemotherapy followed by ASCT. Brentuximab vedotin is accepted by SMC (advice number 845/12) for use in Scotland after failure of ASCT. There is no standard of care following failure of ASCT and brentuximab vedotin. In suitable patients, a second ASCT may be an option or for younger patients with a suitable donor, alloSCT may be possible. In patients unsuitable for transplant combined modality therapy should be considered, especially in patients with early relapse and in those who have not received prior radiotherapy or have relapsed outside of the initial radiotherapy field. In patients unlikely to tolerate the toxicity associated with more intensive regimens, palliation with single-agent or multi-agent oral therapy with or without IV vinblastine should be considered.[7,8]

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely for effective treatment options.

At the September 2016 data cut-off in the pivotal study, pembrolizumab was associated with an ORR of 74% in patients who had failed on brentuximab vedotin after failure of ASCT and 64% in patients who had failed on brentuximab vedotin and were ineligible for ASCT.[2,3] The EMA noted that patients already exposed to brentuximab vedotin (i.e. cohorts 1 and 2) have few or no treatment options and ORR with pembrolizumab in this advanced setting were considered remarkable. It was highlighted that as transplant eligibility relies on achieving pre-transplant remission, patients previously transplant-ineligible due to persistence of residual disease could eventually become eligible following treatment with pembrolizumab, with all the implications on long-term disease control. In this regard, the 25% complete remission rate in patients previously ineligible for ASCT (i.e. cohort 2) was considered clinically relevant.[2]

PFS or overall survival are usually preferred primary outcomes in studies investigating new medicines for haematological malignancies but their interpretation in the absence of a randomised control can be problematic. In this context, ORR was considered by the EMA as an acceptable primary outcome in the KEYNOTE-087 study. Also, there can be limitations with PFS to assess efficacy of medicines (such as PD-1 inhibitors) that act by stimulating the immune system as clinical benefit can be observed after initial progression. Additionally, the impact of the unique histological structure of classical Hodgkin lymphoma (in which, unlike most other neoplasms, the majority of tumour mass consists of non-clonal inflammatory cells) on pseudoprogression is currently poorly characterised and

requires further investigation. In KEYNOTE-087 study 13 patients continued pembrolizumab after an initial assessment of progressive disease and two of them reached a subsequent clinical response.[4]

The open-label design of the clinical studies may limit assessment of subjective outcomes, such as quality-of-life and safety. Absence of a placebo or active control arm limits the interpretation of study outcomes and the studies limited treatment with pembrolizumab to two years.

The evidence base for pembrolizumab in patients ineligible for transplant due to reasons other than chemo-refractory disease is limited. All patients in KEYNOTE-087 who were ineligible for ASCT, were ineligible due to chemo-refractory disease. Across the study programme, which also includes KEYNOTE-013, only four patients were ineligible for ASCT due to advanced age or co-morbidities and one patient refused ASCT. This evidence base does not support definitive conclusions for this group. However, the EMA noted that, taking account of the high unmet need and absence of effective therapies, pembrolizumab should be licensed for all transplant-ineligible patients.[2]

As there were only 18 patients (8.6%) in the KEYNOTE-087 study aged at least 65 years, it is not possible to make definitive conclusions about the efficacy and safety of pembrolizumab in this subgroup. The EMA highlighted that the ORR in these patients at the September 2016 data cut-off was 50% (9/18), whereas it was 71% (136/192) in the younger subgroup. Also, patients with ECOG performance status score of 2 or more were excluded, limiting the application of study results to this patient group.[2]

There were no direct comparative data for pembrolizumab versus standard-of-care. Naïve and matched adjusted indirect comparisons (MAIC) were performed to compare data provided in confidence from the latest data cut-off from KEYNOTE-087 for pembrolizumab and a retrospective observational study (by Cheah et al. 2016)[9] of adults with classical Hodgkin lymphoma who had disease progression after brentuximab vedotin and were treated at one US centre between 2007 and 2015.

In this study, patients received a variety of therapies including investigational agents, chemotherapy, ASCT and combined data from the 79 patients who received these was used to represent standard-of-care. The indirect comparisons suggested improvement in PFS and ORR with pembrolizumab over standard-of-care. The validity of these comparisons were limited by weaknesses, including uncertainty around external validity of the population in Cheah et al. 2016 versus Scottish population, especially in relation to the range of therapies comprising standard-of-care and proportion of patients receiving investigational medicines (35%). There were differences across the studies in duration of follow-up and issues with data immaturity, especially for PFS in cohort 1 of KEYNOTE-087 study. There were differences in definition of response (IWG criteria versus Lugano criteria), although this may have had minimal impact. In the MAIC there may have been unidentified confounding factors not included in the matching process and there was uncertainty around the prognostic value of some factors included. Finally, the comparisons did not include duration of response, quality-of-life and safety outcomes and may have been limited by sample size.

Clinical experts consulted by SMC considered that pembrolizumab is a therapeutic advancement for patients with classical Hodgkin lymphoma who have disease progression on or after brentuximab vedotin and have failed previous ASCT or were transplant-ineligible, due to effects on ORR. They consider that it may be used as a last-line of salvage therapy and may be most useful for patients eligible for stem cell transplant. It was also noted that management of adverse events associated with immunotherapies may be an issue.

At the PACE meeting it was noted that there is substantial unmet need for this group of patients with difficult to treat relapsed or refractory Hodgkin lymphoma who have few or no effective treatment options. Current chemotherapy treatments are often associated with poor response rates and

substantial adverse effects. Pembrolizumab was considered to be in the new class of medicines that offers substantial clinical benefits in terms of response rates. For some patients pembrolizumab may provide a bridge to stem cell transplant, which could effect a cure, with all the subsequent benefits, while other patients may benefit from a strong and durable remission.

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

Patient and clinician engagement

A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of pembrolizumab, as an ultra-orphan in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Hodgkin lymphoma is usually incurable in situations where a patient has relapsed or refractory disease and they have failed ASCT and brentuximab; or who are transplant-ineligible and have failed brentuximab.
- The poor prognosis and lack of effective treatment options can have a psychological impact on patients and their family and carers. There is a particular unmet need in patients who are ineligible for ASCT (due to chemorefractory disease or patient factors such as co-morbidities and age) and pembrolizumab offers a licensed treatment option for this small group of patients.
- Current chemotherapy treatments are often associated with poor response rates and substantial adverse effects. They are often administered in hospital, which can add to the burden on patients and carers.
- Pembrolizumab may be associated with fewer adverse effects than conventional chemotherapies and many treatment centres in Scotland now have experience in managing its adverse effects profile.
- Pembrolizumab is associated with very good response rates, which for some patients may provide a bridge to a stem cell transplant, thereby effecting a potential cure.
- For other patients it may provide a substantial prolonged remission where the patient is essentially well, has a good quality-of-life and is able participate fully in family life, education, work and society. This may reduce the caring demands on family and carers.

Additional Patient and Carer Involvement

We received a patient group submission from the Lymphoma Association, which is a registered charity. The Lymphoma Association has received 6.5% pharmaceutical company funding in the past two years, including from the submitting company. A representative from the Lymphoma Association participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

Value for money

The company presented a cost-utility analysis which compared pembrolizumab against Standard of Care (SoC) in adults with relapsed or refractory classical Hodgkin lymphoma who have either failed ASCT and brentuximab vedotin (cohort 1) or are ineligible for ASCT and have failed brentuximab vedotin (cohort 2). SoC consisted of chemotherapy, bendamustine and investigational agents and a sensitivity analysis versus best supportive care (BSC) was also provided by the company.

The submitting company described the economic model as a short-term decision tree followed by a Markov state transition model. However it is worth noting that the economic model consisted of three main components:

- A partitioned survival model which consisted of three health states: progression-free disease (PF), progressed disease (PD) and death. The partitioned survival model was run for the first 12 weeks of the analysis and estimated the proportion of patients in each health state at 12 weeks.
- A short term decision tree which consisted of two chance nodes and captured the impact of the initial 12 weeks of treatment. The first chance node represented outcomes for PF patients in terms of complete response, partial response and stable disease. PD and death were also included as outcomes within the first chance node of the decision tree. The second chance node represented the uptake of alloSCT at week 12 for patients who were complete or partial responders or with stable disease. The model assumed that no patients in the PD health state could go on to receive alloSCT.
- Two independent Markov state transition models which estimated outcomes associated with patients after 12 weeks who discontinued pembrolizumab or SoC and went on to receive an alloSCT (post-alloSCT pathway) and those who remained on initial treatment and did not undergo an alloSCT (non-alloSCT pathway). The post-alloSCT model consisted of two health states: alive and dead, while the non-alloSCT pathway consisted of three states: PF, PD and death.

The economic model also included a treatment stopping rule for patients who received pembrolizumab. According to the stopping rule patients were treated for a maximum of 24 months.

The sources of the clinical data included KEYNOTE-087, a naïve indirect comparison, clinician surveys and various published sources. In terms of the partitioned survival component of the model the KEYNOTE-087 study was used to estimate OS between 0-12 weeks for both pembrolizumab and SoC and PFS for pembrolizumab. PFS for SoC was estimated by applying a hazard ratio from the indirect comparison to the PFS estimates for pembrolizumab. To estimate the proportion of patients who were complete responders, partial responders or had stable disease for pembrolizumab the model used response rates from the KEYNOTE-087 study; these values were adjusted using the odds ratios for response from the indirect comparison to obtain similar data for SoC. The proportion of patients who received an alloSCT (dependent on response to treatment) was estimated using clinician surveys. PFS for pembrolizumab post 12 weeks in the non-alloSCT pathway was estimated using KEYNOTE-087 data, applying a hazard ratio from the indirect comparison to produce similar data for SoC. Mortality in the pre-progression health state was estimated using general population mortality. Post-progression survival was estimated using data from a published study in both the pembrolizumab and SoC arms of the analysis. Survival for patients who received an alloSCT (post-alloSCT pathway) was estimated using data from a different published study.

Utility values for pembrolizumab in the PF health state were generated by calculating response specific utility values from EQ-5D data collected in the KEYNOTE-087 study and weighting by response to treatment. A similar approach was used for SoC, however the weighting used response rates from a published study. To estimate the utility value for PD, the company applied a decrement taken from a separate published study to the utility value for stable disease. For patients who received alloSCT, separate utility estimates were applied pre- and post-100 days after transplant (to account for reduced quality-of-life immediately post-alloSCT). Utility values post 100 days were estimated by taking the response specific utility values from KEYNOTE-087 and weighting by the response rates derived from a published source. The utility value pre-100 days was estimated by applying a decrement taken from another published study to the post-100 days utility estimate. The economic model also captured disutilities related to adverse events.

Medicines costs were included in the analysis as well as costs of administration, subsequent therapy and supportive care, disease management, adverse events and alloSCT. Duration of treatment with pembrolizumab was estimated using KEYNOTE-087 data, time on treatment (TOT) modelling and application of the stopping rule. Treatment duration for SoC was based on PFS.

A complex patient access scheme was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The base case results and selected sensitivity analyses which include the pembrolizumab PAS are presented in the tables below.

Table 2: Base case results pembrolizumab versus SoC (with pembrolizumab PAS)

Cohort	Incremental Cost	Incremental QALY*	ICER**
Cohort 1	£51,943	1.274	£40,765
Cohort 2	£39,528	0.871	£45,379

*Quality adjusted life year
** Incremental cost-effectiveness ratio

Table 3: Selected sensitivity analysis (with pembrolizumab PAS)

Analysis	Cohort 1	Cohort 2
0% of patients have alloSCT	£67,384	£85,106
Alternative source for alloSCT uptake rates	£59,235	£73,182
Reduce response at week 12 SoC CR odds ratio	£50,045	£68,361
Reduce response at week 12 SoC PR odds ratio	£46,046	£55,062
Lower alternative PR alloSCT rate	£44,767	£52,692
Reduce PFS weeks 0-12 SoC HR	£44,102	£50,882
Using MAIC HR and OR	£34,374	£38,646
Gompertz week 12+ PFS extrapolation in cohort 2	-	£50,012
Remove the stopping rule from the economic model	£50,521	£48,333
Comparison versus BSC	£41,415	£46,195

The main weaknesses were as follows

- The economic analysis is based on a naïve indirect comparison and therefore the hazard ratios for progression-free survival and odd ratios for response used in the model are associated with uncertainty. In addition, an important component of the economic analysis is the availability of alloSCT for a proportion of patients who were initially treated with pembrolizumab or SoC and remained progression free at 12 weeks; however KEYNOTE-087 was not designed as a bridging study and few patients received transplant. Therefore there is a lack of data regarding pembrolizumab patients who underwent an alloSCT to inform the economic analysis.
- The available data used to model the effectiveness of alloSCT are based on 13 patients and it was uncertain how similar these patients may be to those in the supporting clinical data (i.e. KEYNOTE-087 or the published study). In addition, the economic model did not include separate health states for alloSCT progression free and progressed disease. Therefore the analysis did not formally model progression free survival for patients who had received a transplant or estimate the duration of time spent and the associated utility in a progressed disease health state following alloSCT.
- The economic model involved estimating parametric functions at various stages of the analysis. More conservative functions may have been available for use in the economic model which represented a similar fit to the data in terms of goodness of fit statistics. In addition, there were concerns regarding the visual fit of some parametric functions to the available data and it was unclear why different functions would be chosen in cohort 1 and cohort 2 to model the same stage or component of the economic model.

- The economic model included a stopping rule although it is uncertain whether this would be applied in clinical practice.

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

Impact beyond direct health benefits and on specialist services

Patients who respond to pembrolizumab can have a marked improvement in their symptoms and quality of life. As they are generally well while in remission this can reduce the caring duties of family and carers, who may also benefit from being able to spend good quality time with the patient. The patient may be able to return to work, education or carer responsibilities within the family.

Pembrolizumab (which is given in an out-patient setting every three weeks) may have a less intensive dosing regimen compared with some chemotherapies given in an in-patient setting and it may be associated with fewer admissions to hospital to manage adverse events. Many Scottish centres have experience in the administration of pembrolizumab and the treatment of adverse events associated with it, which are considered to be generally manageable and acceptable to patients.

Costs to NHS and Personal Social Services

The submitting company estimated there would be seven patients eligible for treatment with pembrolizumab in all years 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 commercially confidential.**

Conclusion

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 a number of the criteria were satisfied: the potential to bridge to a definitive therapy; and the absence of other treatments of proven benefit. In addition, as pembrolizumab is an ultra-orphan 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 restricted use in NHS Scotland

Additional information: guidelines and protocols

The British Committee for Standards in Haematology (BCSH) and the British Society of Blood and Marrow Transplantation published "Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma" in October 2013. This guideline makes the following recommendations:

- ASCT is the standard treatment for patients with relapsed or primary resistant disease who achieve an adequate response to salvage therapy. ASCT is not recommended in those failing to achieve an adequate response (currently defined as a partial response).
- Current evidence does not support the use of maintenance cytotoxic therapies post-ASCT.
- Allogeneic transplantation using a reduced intensity conditioning regimen is the treatment of choice for younger patients with a suitable donor and chemo-sensitive disease following failure of ASCT.
- A second ASCT is a reasonable clinical option in selected patients with late relapse following ASCT.
- In patients not eligible for ASCT, combined modality therapy should be considered, especially in early stage relapse and in patients who have not received prior radiotherapy or who have relapsed outside of the initial radiotherapy field.
- In patients unlikely to tolerate the toxicities associated with more intensive regimens, palliation with either a single agent or with a multi-agent oral regimen with or without IV vinblastine should be considered.[7]

The European Society for Medical Oncology (ESMO) updated its "Hodgkin's lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up" in 2014. This guideline makes the following recommendations:

- For most patients with refractory or relapsed Hodgkin lymphoma, high-dose chemotherapy followed by ASCT can be regarded as the treatment of choice.
- Salvage regimens such as dexamethasone/high-dose cytarabine/cisplatin (DHAP), ifosfamide/ gemcitabine/vinorelbine/dexamethasone (IGEV) or ifosfamide/carboplatin/etoposide (ICE) are given to reduce the tumour burden and mobilise stem cells prior to high-dose chemotherapy and ASCT.
- Brentuximab vedotin is an option for patients failing ASCT.
- Reduced-intensity conditioning allogeneic SCT (RIC-allo) can be considered in young, chemosensitive patients in good general condition. However, RIC-allo is not a standard approach in Hodgkin lymphoma and should be conducted within clinical trials.
- In a palliative setting, acceptable remission rates, satisfying quality of life and prolonged survival can be achieved by gemcitabine- or bendamustine-based chemotherapy and/or regional radiotherapy. Brentuximab vedotin can also be considered for the treatment of HL patients with disease recurrence after at least two lines of treatment who are not candidates for high-dose chemotherapy followed by ASCT.[8]

Additional information: comparators

There is no standard of care for patients who have failed or are ineligible for ASCT and, after subsequent brentuximab vedotin, experience disease progression. Treatment options include combined modality therapy, a varied range of chemotherapies or best supportive care.

Nivolumab is licensed for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

Cost of relevant comparators

Medicine	Dose regimen	Cost per cycle (£)
Pembrolizumab	**200mg IV infusion every 3 weeks**	**5,260**
Nivolumab	3mg/kg IV infusion every 2 weeks	2,414

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS on 01 November 2017. Cost for nivolumab is based on body weight of 70kg. Costs do not take any patient schemes into consideration.

References

1. Merck Sharp Dohme Ltd. Summary of product characteristics for pembrolizumab (Keytruda®), last updated 1 September 2017.

2. European Medicines Agency. European Public Assessment Report for pembrolizumab (Keytruda®), Committee for Medicinal Products for Human Use (CHMP) assessment report EMA/252426/2017, 23 March 2017.

3. Chen R, Zinzani PL, Fanale MA et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol 2017; 35; 2125-32.

4. *Commercial in Confidence**.

5. *Commercial in Confidence**

6. *Commercial in Confidence**

7. Collins GP, Parker AN, Pocock C, et al. Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma. Br J Haematol 2014; 164: 39-52.

8. Eichenauer DA, Engert A, André M, at al. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 (suppl 3): 70-75.

9. Cheah CY, Chihara D, Horowitz S, et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. Ann Oncol 2016; 27: 1317-23.

This assessment is based on data submitted by the applicant company up to and including 7 December 2017.

**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_statements/Policy_Statements*

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 NHS Scotland 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 NHS Scotland 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.