Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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nivolumab 10mg/mL concentrate for solution for infusion (Opdivo®)
SMC No (1240/17)

Bristol-Myers Squibb Pharmaceuticals Ltd

09 June 2017

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 assessed under the end of life and ultra-orphan process

nivolumab (Opdivo®) is accepted for use within NHS Scotland.

Indication under review: the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

In an open-label, single-arm study, a clinically meaningful objective response rate was achieved in patients with relapsed or refractory cHL treated with nivolumab.

SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost effectiveness of nivolumab and 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

The treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.[1]

Dosing Information

The recommended dose is 3mg/kg administered intravenously (IV) over 60 minutes every two weeks.

Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Refer to the summary of product characteristics for further detail.

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

Product availability date

November 2016.

Nivolumab received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 3 November 2016.

Nivolumab meets SMC ultra-orphan and end of life criteria for this indication.

Background

Nivolumab is a monoclonal antibody which binds to the programmed death-1 (PD-1) receptor found on T-cells. The PD-1 receptor is a negative regulator of T-cell activity which is involved in the control of T-cell immune responses. PD-L1 and PD-L2 are proteins produced by cancer cells that interact with the PD-1 receptor and switch off the activity of T-cells. Nivolumab blocks PD-L1 and PD-L2 from binding to the PD-1 receptor and prevents T-cell deactivation.[1] Hodgkin lymphoma is a lymphoid malignancy characterised by the presence of multinucleated Reed-Sternberg cells. PD-L1 and PD-L2 are over-expressed on Reed-Sternberg cells.[2]

Nivolumab 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 has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

Preferred initial treatment for cHL is chemotherapy with or without radiotherapy. The aim of therapy is to achieve cure. The preferred option for treatment for relapsed Hodgkin lymphoma is high dose chemotherapy, with adiotherapy in appropriate patients, followed by ASCT. Brentuximab vedotin is a treatment option in patients who have failed ASCT. Following failure of brentuximab vedotin treatment options are limited and median overall survival is likely to be less than two years.[2, 3] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, as currently available alternatives have limited efficacy. Nivolumab meets SMC ultra-orphan and end of life criteria for this indication.

A patient and clinician engagement (PACE) meeting was held to consider the added value of nivolumab, as an ultra-orphan medicine, in the context of treatments currently available in NHS Scotland. At the PACE meeting, participants highlighted that relapsed or refractory Hodgkin lymphoma is a highly symptomatic and distressing terminal disease.

Impact of new technology

Summary of evidence on comparative efficacy

The key evidence to support the marketing authorisation was CheckMate 205, an ongoing pivotal phase II, multicentre, non-comparative, multicohort, single-arm study of nivolumab in patients with cHL following failure of ASCT) Patients enrolled into cohort B and C were adults (≥18 years old) with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Patients had documented failure to achieve at least partial remission after the most recent treatment or documented relapse (after complete remission) or disease progression (after partial remission or stable disease) and had received previous high-dose conditioning chemotherapy followed by ASCT as part of salvage therapy.[2, 4] Patients enrolled into cohort B had failed brentuximab vedotin treatment following ASCT and patients enrolled into cohort C had failed brentuximab vedotin treatment before or after ASCT.[2, 4] In cohort A patients were brentuximab vedotin naive and cohort D included patients with newly diagnosed cHL.[2, 5] Cohorts A and D are not discussed further.

All patients received nivolumab 3mg/kg, intravenously (IV) over 60 minutes every two weeks. This continued until disease progression, death, unacceptable toxicity, consent was withdrawn or the end of the study. During the study, an amendment was made to the study protocol which allowed patients to continue treatment beyond investigator-assessed disease progression. This was in cases where there was an atypical clinical response pattern, for example, reduced total tumour burden despite new lesion(s) appearing.[4]

The primary outcome was the proportion of patients with an objective response, defined as best overall response of complete or partial remission using the revised International Working Group (IWG) criteria for Malignant Lymphoma (2007 criteria) and assessed by an independent radiological review committee (IRRC).[4] All patients who received at least one dose of nivolumab were included in the efficacy and safety analysis.[4]

The primary analysis of cohort B was performed at the 20 August 2015 data cut-off date. After median follow-up of 8.9 months, the IRRC-assessed objective response rate was 66% (53/80);

this was complete remission (8.8%, [7/80]) or partial remission (58% [46/80]). The rest of the patients had a best overall response of stable disease (22%), progressive disease (7.5%) or unable to determine (3.8%).[4] The primary analysis for cohort C was performed at the April 2016 data cut-off. After a median follow-up of 8.8 months, the IRRC-assessed objective response rate was 73% (73/100); this was complete remission (17% [17/100]) or partial remission (56% [56/100]).[2]

Table 1 contains the key secondary and exploratory outcomes reported at the primary analysis: 20 August 2015 data cut-off for cohort B and April 2016 data cut-off for cohort C.[2, 4]

Table 1. CheckMate 205: key secondary and exploratory outcomes, minimum six months follow up.

Outcome	Cohort B (n=80)	Cohort C (n=100)
Median IRRC-assessed duration of objective response	7.8 months	7 months
Median IRRC-assessed duration of complete remission	4.6 months	N/A
Median IRRC-assessed duration of partial remission	7.8 months	7 months
Investigator-assessed objective response rate	72% (58/80)	66% (66/100)
Investigator-assessed complete remission	28% (22/80)	26% (26/100)
Investigator-assessed partial remission	45% (36/80)	40% (40/100)
Median investigator-assessed duration of objective response	9.1 months	9.8 months
Median IRRC-assessed progression-free survival	10 months	11.2 months
Progression-free survival rate at six months	77%	77%
Overall survival rate at six months	99%	94%

Updated efficacy from the April 2016 IRRC data cut-off has been reported with a 12-month minimum follow up in cohort B. The IRRC-assessed median duration of response was 13.1 months, progression-free survival was 14.8 months, the 12-month progression-free survival rate was 55% and the 12-month overall survival rate was 95%.[2]

Health-related quality of life was assessed using EQ-5D visual analogue scale (VAS) and European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30 (EORTC-QLQ-C30). Results have been reported for cohort B. The mean EQ-5D VAS score (scale 0 to 100) was 62 at baseline (n=76) and increased over time to 80 at week 33 (n=44). There was a clinically meaningful improvement seen by week 9 (n=62), a 7.9 point change.[4] EORTC QLQ-C30 global health and functional subscales and symptom subscales scores generally remained stable over time. There was a clinically meaningful improvement from baseline in role function at week 9 (10.7), social functioning at week 33 (10.6) and insomnia at week 33 (-12.2).[2, 4] Of the patients who had B-symptoms (fever, night sweats and weight loss) at baseline, 89% (16/18) had complete resolution of symptoms with a median time to resolution of 1.9 months.[2]

CA209039 was a phase I, multi-centre open-label, dose escalation and expansion study. Twenty-three patients with relapsed or refractory cHL were enrolled in an expansion cohort and received nivolumab monotherapy until disease progression or complete remission or for a maximum of two years. After a median follow up of 40 weeks the investigator-assessed objective response rate in the relevant subgroup, patients who had relapsed following ASCT and brentuximab vedotin treatment, was 87% (13/15). Complete remission was observed in one patient (7%), partial remission in 12 patients (80%) and stable disease in two patients (13%). The IRRC-assessed objective response rate in this subgroup was 60% (9/15), with all being partial remission. There were also five patients with stable disease. Progression-free survival at 24 weeks within this subgroup was 85% and median overall survival was not reached at data cut-off.[6]

Summary of evidence on comparative safety

No comparative safety data are available for this indication. The adverse event profile of nivolumab has been characterised within the existing indications and the general safety profile of nivolumab in patients with cHL was consistent with this.[2] Refer to the summary of product characteristics for details.[1]

In cohort B, adverse events were reported in most patients (99%, 79/80); these were grade 1 or 2 in 58% of patients, grade 3 in 33%, grade 4 in 7.5% and one patient died due to multi-organ failure. Treatment-related adverse events were reported in 89% of patients; these were grade 1 or 2 in 64% of patients, grade 3 in 21% and grade 4 in 4%. Serious adverse events were reported in 25% of patients, these were considered treatment-related in 6% of patients. Adverse events leading to treatment discontinuation were reported in three patients.[4]

The most common treatment-related adverse events in cohort B were fatigue (25%), infusion-related reaction (20%), rash (16%), arthralgia (14%), pyrexia (14%), nausea (13%), diarrhoea (10%) and pruritus (10%).[4]

Summary of clinical effectiveness issues

In the pivotal CheckMate 205 study, the IRRC-assessed objective response rate was 66%, which is considered clinically meaningful by the EMA. There were also some clinically meaningful improvements in health-related quality of life from baseline identified, measured by EQ-5D VAS, EORTC-QLQ-C30 and resolution of B symptoms.[2] In cohort B, subgroup analyses were supportive of the primary analyses although some subgroups were too small to draw any definitive conclusions. *Post hoc* subgroup analyses in patients who had failed previous treatment with brentuximab vedotin were also consistent with the primary analyses.[2] Subgroup analysis of cohort C, defined by timing of brentuximab vedotin in relation to ASCT, provided reassurance about efficacy irrespective of sequence of administration. After a protocol amendment, nine patients in cohort B continued nivolumab treatment beyond progression. There were six patients who maintained tumour reduction in target lesions and five of these patients maintained reduced tumour burden following the appearance of new lesions.[4] The marketing authorisation recommends continuing nivolumab as long as the patient is experiencing a clinical benefit or until it is no longer tolerated.[1]

The main limitations to the evidence base are the absence of direct comparative data and the immaturity of the survival data. The single-arm, open-label design of the study could potentially have influenced the results, especially quality of life results. There were differences in IRRC-assessed and investigator-assessed response, in particular the proportion of patients considered to be in complete remission (9% versus 28%, respectively). This may have been due to

interpretation of 18F-fluorodeoxyglucose–positron emission tomography scans and is not considered by EMA to have a meaningful impact on the results.[2]

Early follow up of patients undergoing allogeneic stem cell transplantation (allo-SCT) after previous treatment with nivolumab suggests a higher than expected incidence of acute graft-versus-host-disease and transplant related mortality. Further data are needed, and careful consideration to the potential benefits of stem cell transplantation and the possible increased risk of transplant related complications should be considered case by case.[1] Patients were required to have an ECOG performance status score of 0 or 1, and there is no evidence in patients with worse performance status scores. Patients with active autoimmune disease and symptomatic interstitial lung disease were excluded from clinical studies of cHL. There are limited data in patients ≥65 years of age.[1]Unadjusted and matching-adjusted indirect comparisons (MAIC) were undertaken of nivolumab versus alternative treatment options.

The unadjusted (naïve) indirect comparison of nivolumab versus standard-of-care, (represented by Cheah 2016[3], excluding patients who received investigational agents) was used to inform the base case in the economic analysis. In Cheah 2016, patients received a variety of treatments, the most common being investigational agents, gemcitabine, and bendamustine. Baseline characteristics of the subgroups were not available so in the analysis excluding investigational agents it was assumed that the baseline characteristics of patients enrolled in clinical studies were equivalent to those of the overall population. It seems likely that baseline characteristics would influence whether or not a patient would be included in a clinical study.

In the MAIC, the relevant nivolumab patient-level data were compared with other treatment options in two groups; a post-ASCT, post-brentuximab vedotin population and a post-ASCT (though not necessarily post- brentuximab vedotin) population. The MAIC was used for scenario analyses.

There is not currently a standard treatment option for patients with relapsed or refractory cHL after ASCT and treatment with brentuximab vedotin. Introduction of nivolumab would provide a licensed treatment option in this patient group. Clinical experts consulted by SMC considered that nivolumab is a therapeutic advancement due to its novel mechanism of action and potential to allow patients to be considered for an allo-SCT.

Clinical experts consulted by SMC considered that the introduction of this medicine may impact on the patient and/or service delivery due to its side-effect profile and IV administration schedule. However the patient numbers are likely to be very small.

At the PACE meeting it was noted that there is a high level of unmet need in patients who have gone through all available treatment options. Palliative care offers little or no benefit and chemotherapy is unlikely to be effective in these heavily pre-treated patients.

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

Patient and clinician engagement

A PACE meeting with patient group and clinical specialist representation was held to consider the added value of nivolumab, as an ultra-orphan and end of life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Relapsed or refractory Hodgkin's lymphoma is a highly symptomatic and distressing terminal disease. It can cause debilitating fatigue, cognitive issues, severe drenching night sweats, significant rapid weight loss (>10% of body weight), fevers and intractable itch.
- There is a high level of unmet need in patients who have gone through all available treatment options. Palliative care offers little or no benefit. Chemotherapy is unlikely to be effective, with PACE clinicians estimating response rates around 20% for these heavily pre-treated patients who are more likely to experience side effects due to the cumulative effect of previous treatments.
- PACE participants expressed a view that the response rates seen with nivolumab treatment are unprecedented in such heavily pre-treated patients with Hodgkin's lymphoma. Patients tend to be extremely debilitated with a poor quality of life. Nivolumab treatment may quickly lead to relief from disease symptoms and may provide a dramatic shift in quality of life.
- Nivolumab offers the potential to be a bridge to an allo-SCT. This is a potentially curative treatment option that could make a dramatic difference to patients and have a profound positive impact on physical and psychological health. Many patients are young with the potential for a long and active life, returning to work, education and family life, if they can manage to undergo successful allogeneic transplant.
- Patients unsuitable for allo-SCT may still benefit from receiving nivolumab as a palliative treatment that may give significant and prolonged symptom reduction which cannot be achieved with standard chemotherapy options.
- A potential advantage for patients is the lower toxicity profile associated with nivolumab compared with standard chemotherapy regimens. PACE participants reported experience of patients on treatment who were able to start taking care of themselves, reducing the burden on family or carers and increasing patient independence.

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 5.7% of its 2016 annual organisational income from pharmaceutical company funding, including from the submitting company. A representative from the Lymphoma Association participated in the PACE meeting. The key points of the submission have been included in the full PACE statement.

Value for money

The company presented a cost-utility analysis which compared nivolumab against standard of care (SoC) in the licensed indication. SoC was assumed to consist of chemotherapy (58%), bendamustine (28%) and brentuximab vedotin retreatment (14%). The chemotherapy component of SoC reflected a range of therapies such as doxorubicin, methylprednisolone, cytarabine and cisplatin (ASHAP), gemcitabine, vinorelbine, liposomal doxorubicin (GVD), or ifosfamide,

carboplatin and etoposide (ICE), amongst others. A sensitivity analysis versus best supportive care (BSC) was also provided by the company.

A semi-Markov model was used to assess the cost-effectiveness of nivolumab versus the comparators using a life time horizon, which equated to 40 years. In terms of model structure the model consisted of three health states, pre-progression, post-progression and death. Patients entered the model in the pre-progression health state and patients could either progress to a worse health state or die. Patients were treated with nivolumab or SoC until disease progression, although for costing purposes SoC reflected the median or recommended duration of treatment for the components of SoC from published sources. Patients who were treated with nivolumab or SoC could also discontinue treatment and switch to BSC when progression free due to adverse events, or discontinue due to other reasons. Nivolumab and SoC patients also switched to BSC when they transitioned to the post-progression health state. In the base case analysis patients who received nivolumab or SoC could not go on to receive an allo-SCT.

The sources of the clinical data included pooled data from Cohort B and Cohort C from the CheckMate 205 study, the post autologous SCT and brentuximab vedotin population from CA209-039 and Cheah (2016).[2, 3] The CheckMate 205 and CA209-039 data were used to estimate PFS and OS for nivolumab and, in order to generate longer term PFS and OS estimates, the data were extrapolated using the log-normal and Weibull functions respectively. For SoC, data from the Cheah (2016) study were used to estimate PFS and OS with longer term estimates for both outcomes generated by extrapolating the data using the exponential function. The OS estimate for SoC was adjusted to remove the impact of investigational agents that a proportion of patients received in the Cheah study. Similar sources as above were also used to determine response to treatment; complete response (CR), partial response (PR) and stable disease (SD), for nivolumab and SoC respectively. Discontinuation for reasons other than progression was estimated using the log-normal curve applied to CheckMate 205 data. The company also provided a sensitivity analysis using the results of the MAIC which was not included in the base case economic model.

Utility values for nivolumab in the pre and post progression health states were taken from EQ-5D data collected in the CheckMate 205 study. The utility values for SoC were taken from a published study with adjustments made to reflect response to treatment.[7] The pre-progression health state values were 0.837 and 0.76 for nivolumab and SoC respectively. The post-progression health state values were 0.715 and 0.39 for nivolumab and SoC respectively. Disutilities for adverse events were included in the analysis.

Medicines costs were included in the analysis as well as administration, subsequent therapy, palliative care, disease management and adverse event costs.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

The results of the base case and selected sensitivity analyses without the nivolumab PAS are presented in the tables below.

Table 2. Base case result versus SoC and sensitivity analysis versus BSC

Analysis	Incremental Cost	Incremental QALY	Incremental LY	ICER at list price for nivolumab
Base case versus SoC	£82,814	2.789	2.892	£29,690
Sensitivity analysis versus BSC	£96,268	3.192	3.902	£30,158

Table 3. Selected sensitivity analysis versus SoC

Analysis	ICER at list price for nivolumab
Use SoC utilities for CR, PR and SD and post-progression for both nivolumab and SoC	£51,253
Nivolumab progression utility set to 0.39	£49,511
No discontinuation for other reasons than death or progression	£43,988
Time horizon of 5 years	£43,596
Unadjusted Indirect comparison: all studies (post ASCT and BTX studies)	£36,896
MAIC: all studies (post ASCT and BTX studies)	£35,682
No adjustment for investigational agents	£33,721
Include allo-SCT as a subsequent treatment option	£28,971
Gompertz curve OS nivolumab	£48,575
Patients who progress or discontinue nivolumab follow survival estimates for SoC	£59,764
Combined analysis: Cheah (2016) overall population data, treatment beyond progression, cost of allo-SCT, utility in post-progression health state for both nivolumab and SoC 0.39	£70,520

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

The main weaknesses were as follows:

- The economic evaluation is based on a naive indirect comparison of the data which increases the uncertainty in the analysis. However the company also provided a sensitivity analysis using the MAIC (see Table 3 above). It was unclear if the efficacy of SoC taken from Cheah (2016) appropriately reflected Scottish clinical practice although the company subsequently presented two physician surveys in order to support the suitability of the Cheah study data for use in the economic evaluation.
- There was uncertainty in the survival modelling as data for nivolumab were immature and no treatment waning effects for OS were included in the base case analysis. Weaknesses were also noted in the modelling of PFS and OS for SoC and using data from the overall population in Cheah (2016) was considered more robust than data used in the base case which removed the impact of investigational agents.
- There were limitations with the utility values used in the analysis. No direct data were available to demonstrate that pre-progression or post-progression utility would be different for patients on SoC versus nivolumab.

- In the base case analysis patients treated with nivolumab could not receive an allo-SCT as a subsequent treatment. However the company has provided a scenario analysis which included allo-SCT as a subsequent treatment option (see Table 3 above). In addition, patients in the CheckMate 205 study may have received an allo-SCT which could impact on the survival estimates of the treatments under consideration; however the cost of allo-SCT was not included in the base case analysis. The company provided a combined scenario analysis which addressed a number of uncertainties in the economic case such as; using Cheah (2016) overall population data, modelling treatment beyond progression, including the cost of allo-SCT and utility in post-progression health state for both nivolumab and SoC is 0.39. The results are presented in Table 3 above.

The Committee also considered the benefits of nivolumab 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: a substantial improvement in quality of life; the potential to bridge to a definitive therapy; and the absence of other treatments of proven benefit. In addition, as nivolumab 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 nivolumab for use in NHS Scotland

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

Impact beyond direct health benefits and on specialist services

At the PACE meeting, participants highlighted that patients with relapsed and refractory cHL tend to be extremely debilitated with a poor quality of life. Nivolumab treatment may quickly lead to relief from disease symptoms and could provide a dramatic shift in quality of life. Nivolumab offers the potential to be a bridge to an allo-SCT. This potentially curative treatment option could make a dramatic difference to patients and have a profound positive impact on physical and psychological health.

Many patients are young with the potential for a long and active life, returning to work, education and family life, if they can manage to undergo allogeneic transplant.

The administration, side effects and toxicity profile of nivolumab are manageable. Cancer centres have experience of its use in other indications so there are protocols to help manage the immune-related adverse events. Nivolumab is an out-patient treatment compared with in-patient chemotherapy so would allow patients to spend more time with their family rather than hospital visits/admissions.

Costs to NHS and Personal Social Services

The submitting company estimated there would be 6 patients eligible for treatment with nivolumab in year 1 and 18 patients in year 5. The estimated uptake rate was 100% in year 1 (6 patients) and 100% in year 5 (18 patients).

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.**

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.[8] This guideline makes the following recommendations:

- ASCT is the standard treatment for patients with relapsed disease who achieve an adequate response to salvage therapy or primary resistant disease who achieve an adequate response to salvage therapy.
- ASCT is not recommended in those failing to achieve an adequate 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.
- 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 intravenous vinblastine should be considered.

The European Society for Medical Oncology (ESMO) updated its "Hodgkin's lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up" in 2014.[9] 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.

Additional information: comparators

There is no standard of care following failure of ASCT and brentuximab vedotin. Clinical experts advise that nivolumab could potentially displace third-line chemotherapy, gemcitabine (off-label) or bendamustine (off-label), or best supportive care.

Cost of relevant comparators

Medicine	Dose regimen	Cost per two-week cycle (£)
Nivolumab	**3mg/kg IV infusion every two weeks**	**2,414**

Costs from eMC DM&D on 2 March 2017. The median duration of nivolumab treatment in CheckMate 205 was not reached in any cohort. Cost for nivolumab is based on body weight of 70kg. IV: intravenous. Costs do not take any patient access schemes into consideration.

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This assessment is based on data submitted by the applicant company up to and including 14 April 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 drug 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.