NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pembrolizumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: September 2021

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using pembrolizumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 12 October 2021

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Pembrolizumab is recommended as an option for treating relapsed or refractory classical Hodgkin lymphoma in people aged 3 and older. It is only recommended if:

- they have had an autologous stem cell transplant that has not worked
- they have not had brentuximab vedotin and
- the company provides pembrolizumab according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with pembrolizumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. This decision should be made jointly by the clinician and the child or young person and the child's and young person's parents or carers, where applicable.

Why the committee made these recommendations

Pembrolizumab is an additional treatment option for people with relapsed or refractory classical Hodgkin lymphoma. Clinical trial evidence shows that pembrolizumab delays the condition getting worse. It is not known if people having pembrolizumab live longer, because longer-term evidence from the KEYNOTE-204 trial is not available yet.

Pembrolizumab is a cost-effective use of NHS resources for treating relapsed or refractory classical Hodgkin lymphoma in people who have had an autologous stem cell transplant that has not worked but have not had brentuximab vedotin. So, it is recommended for use in the NHS in this population.

The cost-effectiveness estimates are uncertain in people who have had 2 previous anticancer treatments and have not had an autologous stem cell transplant and brentuximab vedotin. The most plausible cost-effectiveness estimate may be within the range usually considered cost effective or may be much higher. Because of this uncertainty, pembrolizumab cannot be recommended for this population.

2 Information about pembrolizumab

Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, Merck Sharp & Dohme) has a marketing authorisation in the UK 'as monotherapy for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least 2 prior therapies when ASCT is not a treatment option.'

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price is £2,630 for 1 x 100 mg vial (excluding VAT; BNF online accessed September 2021).

The company has a commercial arrangement (simple discount patient access scheme). This makes pembrolizumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by MSD, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

People with classical Hodgkin lymphoma would welcome an effective treatment option that is more tolerable

3.1 The patient expert and a committee member with personal experience of how the condition affects patients' lives explained that classical Hodgkin lymphoma and its treatment substantially affects quality of life. They explained that the physical symptoms which can include fatigue, breathlessness, nausea, fevers, night sweats, weight loss and severe itching are also exacerbated by the emotional effect of the condition. People with classical Hodgkin lymphoma may experience depression, anxiety, isolation and loss of self-esteem. Further consequences can include substantial financial impact because of the inability to work and an inability to care for children. The patient expert explained that pembrolizumab is a desirable treatment option, because it is more tolerable and more convenient than other treatments for classical Hodgkin lymphoma and does not need prolonged hospital stays. They explained that these are important factors for people with the condition. The committee recognised the potential benefits that pembrolizumab may bring for people with classical Hodgkin lymphoma. It concluded that people would welcome a new effective treatment option, especially one that is well tolerated.

Treatment pathway

Pembrolizumab would offer an alternative treatment option to brentuximab vedotin for people who have had 2 previous treatments

3.2 Treatment for classical Hodgkin lymphoma which is relapsed or refractory to first-line chemotherapy is salvage chemotherapy. People whose condition has responded to salvage chemotherapy, and are well enough, may be offered an autologous stem cell transplant.

- For people whose condition is relapsed or refractory to salvage chemotherapy and for whom a stem cell transplant is not suitable, or whose condition is relapsed or refractory to autologous stem cell transplant, NICE's technology appraisal guidance on brentuximab vedotin for treating CD30-positive Hodgkin lymphoma recommends brentuximab vedotin as a third-line treatment option.
- For people who have had an autologous stem cell transplant and brentuximab vedotin, NICE's technology appraisal guidance on nivolumab for treating relapsed or refractory classical Hodgkin lymphoma recommends nivolumab as an option for treating relapsed or refractory classical Hodgkin lymphoma.
- For people who have not had an autologous stem cell transplant and whose condition is relapsed or refractory to third-line brentuximab vedotin, NICE's technology appraisal on pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma recommends pembrolizumab within the Cancer Drugs Fund. The clinical experts noted that although most people have pembrolizumab currently because of its availability though the Cancer Drugs Fund, the routinely commissioned standard care is multi-agent chemotherapy.

The clinical experts explained that some people may be offered an autologous or allogenic stem cell transplant after third- or fourth-line treatment depending on their fitness for transplant and how their condition

has responded to previous lines of therapy. The committee noted that pembrolizumab has previously been appraised for use after brentuximab vedotin in NICE's technology appraisal guidance on pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma. However, its marketing authorisation has now been extended to allow its use as a third-line treatment option, when brentuximab vedotin is currently standard care. The committee concluded that pembrolizumab would potentially offer an alternative to brentuximab vedotin for people who have had 2 previous lines of therapy, with or without a previous stem cell transplant.

Clinical evidence

KEYNOTE-204 subgroup data is generalisable to people who have had 2 previous treatments, with or without previous stem cell transplant

3.3 KEYNOTE-204 is an open-label, randomised controlled trial comparing pembrolizumab with brentuximab vedotin as a treatment for classical Hodgkin lymphoma in adults whose condition is relapsed or refractory to at least 1 previous multi-agent chemotherapy regimen. Participants in KEYNOTE-204 were randomised after stratification into groups who had and had not had previous stem cell transplant. The committee noted that the marketing authorisation for pembrolizumab is narrower than the trial population and includes only people for whom autologous stem cell transplant has not been successful or who have had at least 2 previous treatments when autologous stem cell transplant is not an option. It noted that the population of interest was a subgroup of the whole KEYNOTE-204 population. The clinical experts considered that the trial results for the subgroup corresponding to the marketing authorisation are generalisable to clinical practice. The committee noted that the comparator treatment in KEYNOTE-204 is brentuximab vedotin and NICE recommends brentuximab vedotin for people who have had 2 or more previous treatments (see section 3.2). It concluded that the trial results for this subgroup are generalisable to NHS practice.

Clinical effectiveness

Pembrolizumab improves progression-free survival compared with brentuximab vedotin

3.4 The population in KEYNOTE-204 who had had at least 2 previous treatments, with or without previous stem cell transplant, showed longer median progression-free survival with pembrolizumab than brentuximab vedotin. These data are academic in confidence and cannot be reported here. The committee noted that the subgroups who had and had not had a previous stem cell transplant were not in the statistical analysis plan. But, analysis of these subgroups indicated that median progression-free survival was longer with pembrolizumab than brentuximab vedotin in both of these groups. The clinical experts explained that pembrolizumab may not have the same relative benefit compared with brentuximab vedotin for people with and without previous transplant. This is because, in some people, the lymphoma will not have responded well enough to chemotherapy to allow a stem cell transplant and these people's condition may have a poorer response to further chemotherapy, including brentuximab vedotin. Pembrolizumab is an immunotherapy and is not expected to be affected by previous response to chemotherapy. The data also suggested that overall prognosis is poorer for people who have not had a previous stem cell transplant compared with those who had, with a shorter progression-free survival in both the pembrolizumab and brentuximab vedotin arms. The committee concluded that for people who had had at least 2 previous treatments with or without previous stem cell transplant, pembrolizumab improves progression-free survival.

KEYNOTE-204 overall survival data are not currently available and time to second progression data are immature

3.5 Overall survival data from KEYNOTE-204 are immature and not currently available. Data from KEYNOTE-204 show that time to second progression (time to disease progression while having the next anticancer treatment)

is longer for people having pembrolizumab compared with brentuximab vedotin after 24 months follow up. These data are academic in confidence and cannot be reported here. However, the time to second progression data are immature and the ERG explained that this was a substantial limitation for its use as an indicator of overall survival benefit. The company highlighted that overall survival is a primary outcome in KEYNOTE-204 and that data will be available in the future. The committee concluded that overall survival could not be estimated from the currently available data in KEYNOTE-204 and other evidence sources would be necessary to estimate overall survival.

Pembrolizumab may increase the number of people who might be able to have a stem cell transplant compared with brentuximab vedotin, but data are limited

3.6 The committee was aware that KEYNOTE-204 did not assess if pembrolizumab would increase the number of people who may be able to have an autologous or allogenic stem cell transplant after their third-line treatment. People who had previously not been offered a stem cell transplant because their condition has not responded well to chemotherapy may show improved disease response with third-line treatment and therefore be able to have a stem cell transplant (see section 3.2). The clinical experts stated that although there were limited data, it was plausible that the proportions of people having a stem cell transplant after pembrolizumab will be greater than after brentuximab vedotin. The clinical experts explained that complete remission rates with brentuximab vedotin are around 25% to 30%, which is the population who would be able to have stem cell transplant. The rates of complete remission for pembrolizumab are comparable to those of brentuximab vedotin. However partial remission rates are higher and partial remission duration is usually longer with pembrolizumab, which may allow more stem cell transplants. The clinical experts also highlighted the possibility that pembrolizumab treatment increases toxicity to allogenic stem cell

transplant and may reduce the effectiveness of autologous stem cell transplant but evidence on this is still emerging. Despite this, the clinical experts suggested that stem cell transplant would be an option for some people after pembrolizumab in clinical practice. The committee concluded that in practice, pembrolizumab may increase the number of people who are able to have a stem cell transplant compared with brentuximab vedotin, but data are limited.

NHS England policy is to fund medicines for children within a specialised service when NICE recommends a technology for adults

3.7 The committee was aware that the marketing authorisation for this indication includes children aged 3 and older, but that KEYNOTE-204 only included adults. The single-arm study KEYNOTE-015 assessed the safety and efficacy of pembrolizumab in children but the company did not include this data in its model. The company stated that this was because NHS England policy is to fund medicines for children within a specialised service if it is recommended for use in adults by a NICE technology appraisal (when the medicine has a licence for use in children and both the indication for use and the age of the child fall within those specified in the adult licence). The committee concluded that children should not be excluded from the recommendations in line with the marketing authorisation for this indication.

Company's economic model

The company's model structure is appropriate for decision making

3.8 The company presented a 3-state partitioned survival model to estimate the cost effectiveness of pembrolizumab compared with brentuximab vedotin. The 3 health states were progression-free survival, progressed disease and death. The committee discussed that previous appraisals for classical Hodgkin lymphoma had used a 4-state model and included stem cell transplant as a health state. The company highlighted that

pembrolizumab was not positioned as a 'bridge to transplant' and therefore used a 3-state model. The company assumed equal rates of stem cell transplant in both the pembrolizumab and brentuximab vedotin arms in its model, including the costs of stem cell transplant but not the impact of stem cell transplant on survival or quality of life. The committee discussed that pembrolizumab may increase the number of people who are able to have a stem cell transplant (see section 3.6) and therefore may be considered a 'bridge to transplant' in practice. However, it concluded that the company's model was adequate for decision making.

It is appropriate to consider people who have had 2 previous treatments with and without previous stem cell transplant separately

3.9 In its original submission, the company presented cost-effectiveness estimates for a pooled population of people who had and had not had a stem cell transplant, as well as estimates for people who had and who had not had a stem cell transplant separately. The company presented a model at technical engagement which only included a pooled population of people who have had 2 previous treatments either with or without previous stem cell transplant. The committee discussed that this was the population of interest from KEYNOTE-204 (see section 3.3). However, the ERG suggested that people who have had 2 previous treatments with previous stem cell transplant and people who have had 2 previous treatments without previous stem cell transplant should be considered separately in the model. This is because the treatment pathway is different for these groups and the prognosis of these groups is also expected to be different. The ERG presented an economic analysis based on these subgroups. The clinical experts agreed that prognosis for people with a previous stem cell transplant may be expected to be better than for people without a previous stem cell transplant and that the subsequent treatment options for these subgroups also differ. The committee discussed that the estimates of costs included in the model may be affected by the different subsequent treatments for each subgroup and

that these groups may also have different prognosis, affecting the survival outcomes included in the model. Therefore, it concluded that it was appropriate to consider the subgroups of people who have had 2 previous treatments with and without previous stem cell transplant separately.

Assumptions in the economic model

For people who have had 2 previous treatments without previous stem cell transplant, the routinely available treatment after brentuximab vedotin is multi-agent chemotherapy

3.10 The ERG highlighted that different subsequent treatments are offered after third-line treatment has not worked, depending on if a person has had a previous stem cell transplant (see section 3.9). The clinical experts explained that:

- people who have previously had a stem cell transplant and had brentuximab vedotin as third-line treatment would usually be offered nivolumab.
- people who have not previously had a stem cell transplant and had brentuximab vedotin as third-line treatment would currently be offered pembrolizumab, which is available through the Cancer Drugs Fund. The committee was aware of NICE's position statement that drugs available through the Cancer Drugs Fund should not be included in economic models. The clinical experts explained that in the absence of pembrolizumab, multi-agent chemotherapy is the only option for subsequent treatment in routine commissioning. They highlighted that the choice for type of multi-agent chemotherapy differs, but that single agent bendamustine is no longer considered suitable.
- for people who would have pembrolizumab as a third-line treatment, brentuximab vedotin is likely to be given as the next treatment, both for people who have, and have not had a previous stem cell transplant.

The committee concluded that the most appropriate subsequent treatments to include in the model were likely to be those described by the clinical experts, which included multi-agent chemotherapy, and not bendamustine, after brentuximab vedotin for people who have had 2 previous treatments without previous stem cell transplant.

Estimates of overall survival are highly uncertain, particularly for people who have not had a stem cell transplant

3.11 Overall survival data from KEYNOTE-204 are not available (see section 3.5). Therefore, the company used overall survival data in its model from Gopal et al. 2015, a single-arm trial of brentuximab vedotin in people with a previous stem cell transplant. The company applied the overall survival data from Gopal et al. to the pembrolizumab and brentuximab vedotin arms in the model, assuming equal overall survival with both treatments. The company suggested that this was a conservative approach to modelling overall survival. The clinical experts explained that pembrolizumab may lead to increased overall survival compared with brentuximab vedotin when offered to people who have had 2 previous treatments, based on their experience of using immunotherapies and the data from KEYNOTE-204 which indicates durable remission is achieved with pembrolizumab. The ERG agreed that Gopal et al. was appropriate to estimate overall survival for people who have had 2 previous treatments with previous stem cell transplant, but that it was not appropriate for people who have had 2 previous treatments without previous stem cell transplant. It preferred to estimate overall survival for this population using data from Balzarotti et al. 2016, a randomised controlled trial of chemotherapy in people who had had 1 previous line of treatment without stem cell transplant, which included an ifosfamide, gemcitabine and vinorelbine (IGEV) regimen treatment arm. The ERG used data from the IGEV arm in Balzarotti et al. to estimate overall survival and also assumed equal overall survival in the pembrolizumab and brentuximab vedotin arms in its model. The

committee considered that KEYNOTE-204 overall survival data would be preferable to using external data sources, but this was not yet available. In the absence of overall survival data from KEYNOTE-204, the committee agreed that it was not known what estimate of overall survival was appropriate to use for the cost-effectiveness estimate. The committee agreed that assuming equal effectiveness with another treatment may be conservative, but there were no available overall survival data to determine if this was the case. Even if this assumption were accepted, it is also uncertain if for the people who had not had a stem cell transplant, data from Gopal et al. or from Balzarotti et al. would be more appropriate. It concluded that the overall survival estimates used in the model are highly uncertain, particularly for people who have not had a stem cell transplant.

Post-progression health-state utility values are uncertain

3.12 The company presented health-related quality of life data from KEYNOTE-204 for the pooled population who had had at least 2 previous treatments with and without previous stem cell transplant. This indicated that health-related quality of life in people whose condition progressed after having pembrolizumab is better than for people whose condition progressed after having brentuximab vedotin. The ERG noted that this was uncertain, because of small patient numbers and the data being collected over a short follow up of 30 days after stopping treatment. It highlighted that this time may not be long enough to capture the true progressed disease state utility values. Therefore, the ERG's preferred assumptions included equal post-progression utilities for both arms, based on the values reported for brentuximab vedotin in the pooled population who have had at least 2 previous treatments with and without previous stem cell transplant. The clinical experts explained that they may expect health-related quality of life to be better in people whose condition progressed after having pembrolizumab compared with people whose condition progressed after having brentuximab vedotin. This is because

brentuximab vedotin is associated with higher rates of side effects, including neuropathy, which can be debilitating and persist for several months. The committee agreed that some side effects of brentuximab vedotin may persist after stopping treatment, but it was difficult to quantify the expected difference in health-related quality of life between the treatment arms over the long term because of the methods used to collect utility data in KEYNOTE-204. It agreed that a better long-term utility in the progressed state for pembrolizumab compared with brentuximab vedotin was unproven. It concluded that the post-progression health-state utility values for pembrolizumab are uncertain but that it was unlikely that the health-state utility values estimated in KEYNOTE-204 would persist for the whole period of progression. Therefore, the committee preferred the ERG's assumption of equal pembrolizumab and brentuximab vedotin post-progression utilities, although it recognised this may be conservative.

The ERG and company used different data cut-points for extrapolation of progression-free survival and time on treatment

3.13 To estimate progression-free survival from data in KEYNOTE-204, the company extrapolated Kaplan–Meier data from a 52-week cut-point. The ERG suggested that a 26-week cut-point was more appropriate, based on the break in the hazards in the data at this point, and included this cut-point in its exploratory analysis. The company also used a piecewise model to extrapolate time on treatment from KEYNOTE-204 data, using an 80-week cut-point. The ERG noted that time on treatment should be largely similar to progression-free survival, because progression often triggers a change in treatment. Therefore, it suggested it is appropriate to use the same cut-point for time on treatment and progression-free survival extrapolation and included a 26-week cut-point for time on treatment in its exploratory analysis. The committee noted the different assumptions preferred by the company and the ERG for extrapolating progression-free survival and time on treatment data and concluded that using different cut-points affected the cost-effectiveness estimates.

Cost-effectiveness estimate

Pembrolizumab is less costly and more effective than brentuximab vedotin in the subgroup of people who have had 2 previous treatments with previous stem cell transplant

3.14 The committee agreed that its preferred approach was to consider people who have had 2 previous treatments with and without previous stem cell transplant separately (see section 3.9). The company presented separate analyses for this subgroup in its original submission. However, at technical engagement the company only presented cost-effectiveness estimates for the pooled population of people with or without previous stem cell transplant. For people with previous stem cell transplant, the ERG exploratory analysis (and the analyses provided by the ERG using the relevant company assumptions from the original submission where these differed to the ERG's) indicated that pembrolizumab dominated brentuximab vedotin, that is pembrolizumab was cost saving and was associated with a greater quality-adjusted life year gain than brentuximab vedotin. Pembrolizumab dominated brentuximab vedotin in all scenario analyses presented by the ERG for this subgroup.

The cost effectiveness for the subgroup of people who have had 2 previous treatments without stem cell transplant is highly uncertain

3.15 The company presented separate cost-effectiveness analyses for the subgroup of people who have had 2 previous treatments without previous stem cell transplant in its original submission. However, it did not provide these subgroup analyses at technical engagement. The committee considered results for this subgroup in which the ERG had implemented the company assumptions from the company's original submission, updated with changes the company had made to the model during technical engagement for the pooled population of people who have had 2 previous treatments either with or without previous stem cell transplant. The assumptions for this subgroup were:

- Both the company and ERG assumed bendamustine would be the next treatment after brentuximab vedotin.
- The company preferred data from Gopal et al. 2015 to estimate overall survival; the ERG preferred data from Balzarotti et al. 2016 (see section 3.11).
- The company used post-progression utility data from KEYNOTE-204 for both arms; the ERG used the same post-progression utilities in both treatment arms (see section 3.12)
- The company used a 52-week cut-point for extrapolating data on progression free survival; the ERG used a 26-week cut point (see section 3.13).
- The company used an 80-week cut-point for extrapolating time on treatment; the ERG used a 26-week cut point (see section 3.13).
- The company assumed 98% dose intensity in both treatment arms; the ERG assumed 100% dose intensity.

The committee concluded that the assumption of bendamustine as a subsequent treatment after brentuximab vedotin was not appropriate, and multi-agent chemotherapy was more appropriate (see section 3.10). However, it agreed that assuming multi-agent chemotherapy instead of bendamustine was unlikely to have a significant effect on the cost-effectiveness estimates. It also agreed that the assumptions on overall survival were highly uncertain (see section 3.11), that post-progression utility estimates were uncertain (see section 3.12) and that there were different options for cut-points to extrapolate data on progression-free survival and time on treatment (see section 3.13). The committee agreed that it was not possible to be confident that either the ERG's or the company's assumptions in this subgroup were accurate. It concluded the cost effectiveness of pembrolizumab for the subgroup of people who have had 2 previous treatments without stem cell transplant is highly uncertain.

The most plausible ICER for the subgroup of people who have had 2 previous treatments without previous stem cell transplant may fall within the range usually considered cost effective, or be much higher

3.16 The analysis provided by the ERG using the company's assumptions in the subgroup of people without previous stem cell transplant resulted in an incremental cost-effectiveness ratio (ICER) which was within the range usually considered cost effective. The ERG's preferred assumptions resulted in an ICER well above the range usually considered cost effective. The ICERs cannot be reported here because of confidential commercial arrangements for brentuximab vedotin. The committee appreciated that it was highly uncertain which assumptions were most appropriate, particularly those related to overall survival and post-progression health-related quality of life estimates. The committee concluded that the most plausible ICER for the subgroup of people who have had 2 previous treatments without previous stem cell transplant is likely to be between the ICER for the analysis presented by the ERG based on the company's assumptions in this subgroup and the ERG's preferred exploratory analysis for this subgroup.

Pembrolizumab is recommended for routine use in the NHS for treating classical Hodgkin lymphoma in people with previous stem cell transplant who have not had brentuximab vedotin

3.17 The committee noted that all relevant analyses for the subgroup of people who have had 2 previous treatments with previous stem cell transplant showed that pembrolizumab dominated brentuximab vedotin (see section 3.14). The committee concluded that pembrolizumab was a cost-effective use of NHS resources in this population and it recommended pembrolizumab as an option for treating relapsed or refractory classical Hodgkin lymphoma in people whose condition has relapsed after or is refractory to autologous stem cell transplant and have not had

brentuximab vedotin, only if the company provides pembrolizumab according to the commercial arrangement.

Pembrolizumab is not recommended for routine use in the NHS for treating classical Hodgkin lymphoma in people who have had 2 previous treatments without previous stem cell transplant

3.18 The committee noted that the ICER range for people who have had 2 previous treatments without previous stem cell transplant was highly uncertain and included cost-effectiveness estimates which were not within the range usually considered a cost-effective use of NHS resources. It noted that the lowest ICER within the plausible ICER range was within the range which is usually considered cost effective, but this was highly uncertain (see section 3.16). Therefore, the committee concluded that it could not recommend pembrolizumab for routine NHS use for treating classical Hodgkin lymphoma in people who have had at least 2 previous therapies and have not had autologous stem cell transplant or brentuximab vedotin.

Cancer Drugs Fund

Pembrolizumab for people who have had 2 previous treatments without previous stem cell transplant meets the Cancer Drugs Fund criteria, but a managed access agreement was not agreed

3.19 Having concluded that pembrolizumab could not be recommended for routine use for people who have had 2 previous therapies and have not had brentuximab vedotin, the committee then considered if it could be recommended as treatment for this population within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). It noted that:

- overall survival data used in the economic model was highly uncertain, based on external data and may have been a conservative estimate.
- different data cut-points for progression-free survival and time on treatment were preferred by the company and the ERG.
- KEYNOTE-204 is still ongoing and direct trial data could help reduce uncertainties about overall survival and extrapolation of progression-free survival and time on treatment.
- the Systemic Anti-Cancer Therapy dataset could provide additional survival data.
- the committees preferred ICER may fall within a range which is usually considered cost effective or may be much higher. The high levels of uncertainty in estimates of overall survival means that pembrolizumab has plausible potential to be cost effective.

The committee concluded that pembrolizumab met the criteria to be considered for inclusion in the Cancer Drugs Fund for this population. However, following the committee meeting a managed access agreement could not be agreed between the company and NHS England for access to pembrolizumab for the time it would be offered within the Cancer Drugs Fund. Without this agreement, it was not possible to recommend pembrolizumab within the Cancer Drugs Fund.

Innovation

The model is adequate to capture the benefits of pembrolizumab

3.20 The company considers pembrolizumab to be innovative. It suggested that pembrolizumab use as a third-line treatment is a step-change in the management of classical Hodgkin lymphoma. The clinical experts agreed that PD-L1 inhibitors such as pembrolizumab are innovative medicines. However, they highlighted that pembrolizumab and other PD-L1 inhibitors are currently available at other stages in the treatment pathway. The committee considered that the model included all health-related quality of

life benefits. It concluded that it had not been presented with evidence of any additional benefits from pembrolizumab as third-line treatment that had not already been included.

Other factors

3.21 No equality or social value judgements issues were identified.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE

technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has classical Hodgkin lymphoma and the doctor responsible for their care thinks that pembrolizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

5.2 If the evidence allows, consideration may be given to an early partial review of this guidance for people who have had 2 previous treatments without previous stem cell transplant. This may be combined with the review of the NICE recommendation for pembrolizumab within the Cancer Drugs Fund in NICE's technology appraisal on pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma which would be conducted as a single technology appraisal of both lines of therapy. NICE welcomes comment on this proposal.

Jane Adam
Chair, appraisal committee A
September 2021

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Albany Meikle
Technical lead

Mary Hughes
Technical adviser

Thomas Feist
Project manager

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