NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

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 recommended if they have had an autologous stem cell transplant that has not worked or they have had at least 2 previous therapies and an autologous stem cell transplant is not an option, and only if:

- they have not had brentuximab vedotin and
- the company provides pembrolizumab according to the commercial arrangement.

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. The effect of pembrolizumab on how long people live is not known 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 and in people who have had at least 2 treatments, have not had an autologous stem cell transplant and have not had brentuximab vedotin. So, it is recommended for use in the NHS in these populations.

2 Information about pembrolizumab

Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, MSD) 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 for pembrolizumab.

Price

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

2.4 The company has a commercial arrangement. 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, reviews of these submissions 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 people's 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 of pembrolizumab 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 at least 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 who are well enough, may have an autologous stem cell transplant. NICE's technology appraisal guidance on brentuximab vedotin for treating CD30-positive Hodgkin lymphoma recommends brentuximab vedotin for people whose condition has relapsed after transplant, or who have had at least 2 previous therapies and for whom a stem cell transplant is not suitable. This broadly corresponds with the patient population for this appraisal. Pembrolizumab is recommended within the Cancer Drugs Fund as an option for people who have not had an autologous stem cell transplant and whose condition is relapsed or refractory to brentuximab vedotin (see NICE's technology appraisal guidance on pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma). The clinical experts noted that although most people are able to have pembrolizumab after brentuximab vedotin 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 allogeneic 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 instead of brentuximab vedotin. The committee concluded that pembrolizumab would potentially offer an alternative to brentuximab vedotin for people who have had at least 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 at least 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 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), although it noted that brentuximab vedotin could be used for longer in KEYNOTE-204 than allowed in its marketing authorisation. The clinical experts considered that the trial results for the subgroup corresponding to the marketing authorisation are generalisable to clinical practice. The committee 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 at least 2 previous treatments, with or without previous stem cell transplant, showed longer median progression-free survival with pembrolizumab than brentuximab vedotin (median progression-free survival 54.7 weeks [95% confidence interval 37.7 to 84.3] compared with 35.7 weeks [95% confidence interval 24.4 to 38.1]). The committee noted that the subgroups who had and had not had a previous stem cell transplant were not in the statistical analysis plan. However, analysis of these subgroups indicated that median progression-free survival was longer with pembrolizumab than

brentuximab vedotin in both 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, which is a targeted chemotherapy. Pembrolizumab is an immunotherapy with a different mechanism of action 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 in this group. 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. 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 KEYNOTE-204 showed that a similar proportion of people in the pembrolizumab (20.3%) and brentuximab vedotin (22.4%) arms went on to have autologous stem cell transplant at any point during follow up. However, of the people who had a stem cell transplant in the brentuximab vedotin arm, some had also had PD-1 inhibitor treatment (pembrolizumab or nivolumab) before a stem cell transplant was done. The committee was also aware that KEYNOTE-204 was not designed to assess if pembrolizumab would result in more people having a stem cell transplant compared with brentuximab vedotin. The clinical experts stated that the population who had not had a previous stem cell transplant would include both people who were not fit enough to have a transplant and people whose condition had not responded well enough to chemotherapy to have a transplant. The group whose condition had not responded to chemotherapy may show improved disease response with a third treatment with a different mechanism of action, and therefore be able to have a subsequent stem cell transplant. They stated that although there was 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 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 allogeneic stem cell transplant but noted that evidence on this is still emerging. They highlighted that this is only applicable to allogeneic stem cell transplant and that autologous stem cell transplant would usually be the preferred treatment option after pembrolizumab or brentuximab vedotin for people who are fit for transplant. The committee concluded that in practice, pembrolizumab may increase the number of people who are able to have an autologous stem cell transplant compared with brentuximab vedotin, but data is 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' in KEYNOTE-204 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 did not model the impact of stem cell transplant on survival or quality of life. The clinical experts stated that pembrolizumab was likely to be used as a bridge to transplant in people whose disease responds adequately and who are fit enough (see section 3.6). The committee discussed that pembrolizumab may increase the number of

people who are able to have a stem cell transplant (see section 3.6) but noted that the model did not capture the costs and benefits of pembrolizumab used as a bridge to transplant. However, it concluded that the company's model was adequate for decision making.

It is appropriate to consider people who had and had not had a 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 had and had not had a 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 and the company presented a separate analysis for people who had had 2 previous treatments without previous stem cell transplant in response to the appraisal consultation document. The clinical experts agreed that the subsequent treatment options for these subgroups differ and that prognosis is poorer for people who are not fit for transplant because of age or comorbidities. However, they noted that the group without previous stem cell transplant also included people who were considered fit for transplant but had been previously not been able to have one only because their disease had not responded well enough to chemotherapy, so did not necessarily have a poorer prognosis. The committee was aware that the estimates of costs included in the model may be affected by different subsequent treatment pathways. It concluded that it was appropriate to consider the subgroups of people who have had and have not had a previous stem cell transplant separately.

Assumptions in the economic model

For people who have not had a 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 of multi-agent chemotherapy differs, but that single agent bendamustine, which was included in the company's model at the first committee meeting, is no longer considered suitable. In response to the appraisal consultation document, the company updated its model for this subgroup and included subsequent treatments in line with those described by the clinical experts.
- If pembrolizumab were available as a third-line treatment, brentuximab vedotin would be 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 company's updated approach to modelling subsequent treatments using multi-agent chemotherapy after brentuximab vedotin was appropriate for people who have had 2 previous treatments without a previous stem cell transplant.

Overall survival estimates are uncertain, but Gopal et al. (2015) is a reasonable source of data for people who have had a stem cell transplant

3.11 Overall survival data from KEYNOTE-204 are not available (see section 3.5). In its analysis of the pooled population of people who have had 2 previous treatments with and without stem cell transplant (see section 3.9), the company used overall survival data in its model from Gopal et al., a single-arm trial of brentuximab vedotin in people with a previous stem cell transplant. The company applied 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 ERG stated that Gopal et al. was appropriate to estimate overall survival for people who have had a previous stem cell transplant because the participants in Gopal et al. had all had previous stem cell transplant and a median of 2.5 previous lines of therapy. The committee considered that KEYNOTE-204 overall survival data would be preferable to using external data sources, but this was not yet available. It discussed that the company's assumption of equal overall survival with both treatments for this group was likely to be conservative and noted that the company did not provide further analysis for this subgroup in response to the appraisal consultation document. The committee concluded that in the absence of overall survival data from KEYNOTE-204, overall survival estimates are uncertain but Gopal et al. is a reasonable source for people who have had a previous stem cell transplant.

It is likely that pembrolizumab is associated with an overall survival benefit for people who have not had a previous stem cell transplant

3.12 At the first committee meeting, the company assumed equal overall survival in both treatment arms and modelled this using data from Gopal et al. (2015) for a pooled population of people who have had at least 2 previous treatments with and without stem cell transplant (see section 3.11). In response to the appraisal consultation document, the company addressed only the population who had not had stem cell transplant and updated its model to include an overall survival benefit for

this group. The company stated that it agreed with the committee's conclusion at the first committee meeting that its initial approach of assuming equal overall survival was conservative, given that there was a progression-free survival benefit for pembrolizumab compared with brentuximab vedotin in KEYNOTE-204. Assuming equivalent overall survival meant that people were modelled to die at a faster rate once the disease progressed if they had pembrolizumab than if they had brentuximab vedotin before progression. The clinical experts did not consider this to be plausible, noting people may actually live longer with progressed disease after pembrolizumab than after brentuximab vedotin because pembrolizumab can have disease modifying effects which last after disease progression. The clinical experts stated that the potential for pembrolizumab to increase the proportion of people who would go on to have potentially curative stem cell transplant (see section 3.6) would also be expected to improve overall survival with pembrolizumab compared with brentuximab vedotin. The committee concluded that although there was no trial overall survival data, it was plausible that there would be an overall survival benefit of pembrolizumab compared with brentuximab vedotin in people who had not had a stem cell transplant.

The size of overall survival benefit for people without previous stem cell transplant is highly uncertain

3.13 To estimate overall survival for pembrolizumab the company used data from a stem cell ineligible cohort of KEYNOTE-087, a single-arm trial of pembrolizumab in people who had had at least 3 previous treatments (a later line of therapy than KEYNOTE-204). An alternative estimate used data from the Systemic Anti-Cancer Therapy (SACT) database for people who had pembrolizumab as fourth-line treatment, which is currently funded through the Cancer Drugs Fund. To estimate overall survival for brentuximab vedotin the company used data from Eyre et al. (2017), a UK-based, retrospective observational study of brentuximab vedotin in people who had 2 previous treatments without previous stem cell transplant. The ERG highlighted that the KEYNOTE-087 data was immature and highly uncertain as well as being in a later line of therapy than KEYNOTE-204. The clinical experts stated that the overall survival benefit presented by the company comparing KEYNOTE-087 with Eyre et

al. was likely to be over-estimated. The committee noted that using the SACT data to estimate overall survival in the pembrolizumab arm reduced the modelled overall survival benefit, giving a more plausible estimate. The committee concluded that the size of benefit for people without previous stem cell transplant is highly uncertain.

Post-progression health-state utility values are uncertain

3.14 At the first committee meeting, 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. In response to the appraisal consultation document, the company updated its preferred assumption for the post-progression utility value after pembrolizumab, using the post-progression utility value from a trial of nivolumab. The updated value was lower than the post-progression utility after pembrolizumab seen in KEYNOTE-204 but was higher than the ERG's approach of assuming equal post-progression utility values for pembrolizumab and brentuximab vedotin. 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 in some people. They explained that the severity of side effects is associated with time on treatment, which is likely to be longer for people for whom stem cell transplant is not suitable. They explained that the side effects associated with pembrolizumab have less

effect on quality of life. The committee agreed that some side effects of brentuximab vedotin may persist after stopping treatment, but it was difficult to quantify any 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 company's approach to estimating the proportion of people who have subsequent treatment is appropriate

3.15 In response to the appraisal consultation document, the company updated its model to include a new approach to calculating the number of people who would have subsequent treatment in the population without previous stem cell treatment. This was calculated by considering the proportion of people whose disease had progressed but who had not died in each model cycle. Of these people, the proportion who would have subsequent treatment was assumed to reflect the proportion of people who had subsequent treatment in each arm of KEYNOTE-204 (these data are academic in confidence and cannot be reported here). The clinical experts noted that the proportions of people having subsequent treatment in each arm of KEYNOTE-204 was approximately what is seen in clinical practice. The committee concluded that the company's approach to estimating the proportion of people who have subsequent treatment, using data from KEYNOTE-204, was appropriate.

Cost-effectiveness estimate

Pembrolizumab is less costly and more effective than brentuximab vedotin in people who have had a previous stem cell

transplant

3.16 The committee agreed that its preferred approach was to consider people who have had and have not had a previous stem cell transplant separately (see section 3.9). The company presented separate analyses for this subgroup in its original submission. However, at the first committee meeting, after an update to the model 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.

Pembrolizumab is cost effective in the subgroup without previous stem cell transplant if a relatively small overall survival benefit is assumed

3.17 In response to the appraisal consultation document, the company updated its model to include separate analysis of people who have had 2 previous treatments without stem cell transplant. The assumptions made by the company at the second committee meeting for this subgroup were:

- multi-agent chemotherapy is the subsequent treatment after brentuximab vedotin (see section 3.10)
- using KEYNOTE-087 to estimate overall survival for the pembrolizumab arm and Eyre et al. to estimate overall survival for the brentuximab vedotin arm, resulting in an overall survival benefit for pembrolizumab (see section 3.13)
- using post-progression utility data from KEYNOTE-204 for the brentuximab vedotin arm and post-progression utility data from a trial of nivolumab for the pembrolizumab arm (see section 3.14)

- calculating the number of people for whom subsequent treatment is suitable in each cycle based on progression-free survival (see section 3.15)
- using each arm of the KEYNOTE-204 data to estimate the proportion of people having subsequent treatment after progression (see section 3.15).

The company base case gave an incremental cost effectiveness ratio (ICER) of under £20,000 per quality-adjusted life year (QALY) gained. The exact ICERs cannot be reported because of confidential commercial arrangements for comparator and subsequent treatments.

The ERG did not present its preferred assumptions for the subgroup of people who have had 2 previous treatments without previous stem cell transplant at the second committee meeting. Instead, it presented several scenario analyses for this subgroup, including a scenario which assumed equal overall survival in both arms, using data from Eyre et al. The committee recalled its conclusion that pembrolizumab is associated with an overall survival benefit but that the size of this is uncertain (see section 3.12 and section 3.13). At the request of the committee the ERG provided a threshold analysis, to show the effect of increasing the overall survival benefit in increments. It did this by applying a series of hazard ratios to the modelled overall survival with brentuximab vedotin to model overall survival scenarios with pembrolizumab. This analysis also included the following assumptions:

- using multi-agent chemotherapy as subsequent treatment after brentuximab vedotin
- using the same post-progression utility values in both treatment arms
- calculating the number of people for whom subsequent treatment is suitable in each cycle based on progression-free survival exits
- using each arm of the KEYNOTE-204 data to estimate the proportion of people having subsequent treatment after progression

- using a 26-week cut-point for extrapolating data on progression-free survival and time on treatment.

The committee concluded that the assumptions used by the ERG in its threshold analysis were appropriate. It considered the results of the threshold analysis, which showed that the ICER for pembrolizumab compared with brentuximab vedotin was under £30,000 per QALY gained if a relatively small overall survival benefit with pembrolizumab was assumed. The committee noted that the ICER was under £20,000 per QALY gained when the overall survival benefit seen in the company's analysis using SACT data for pembrolizumab was reached in the threshold analysis, which it considered to be the most plausible of the scenarios presented by the company (see section 3.13). The committee concluded that plausible assumptions of an overall survival benefit with pembrolizumab compared with brentuximab vedotin resulted in an ICER below £30,000 per QALY which represented a cost-effective use of NHS resources.

Pembrolizumab is recommended for treating classical Hodgkin lymphoma in people with previous stem cell transplant

3.18 The committee noted that all relevant analyses for the subgroup of people who have had a previous stem cell transplant showed that pembrolizumab dominated brentuximab vedotin (see section 3.16). The committee concluded that pembrolizumab was a cost-effective use of NHS resources in this population. 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 recommended for treating classical Hodgkin lymphoma in people who have not had a previous stem cell transplant

3.19 The committee noted that the threshold analysis presented by the ERG showed that pembrolizumab could be considered cost effective when a

relatively small overall survival benefit was assumed (see section 3.17). It concluded that pembrolizumab was associated with an overall survival benefit (see section 3.12) and therefore that it was likely that pembrolizumab was a cost-effective use of NHS resources in this population. Therefore, the committee recommended pembrolizumab as an option for treating classical Hodgkin lymphoma in people for whom autologous stem cell transplant is not a treatment option and who have had at least 2 previous therapies which has not included brentuximab vedotin.

Innovation

The model is adequate to capture the benefits of pembrolizumab

3.20 The company considers pembrolizumab to be innovative. It suggested that using pembrolizumab 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 noted that the company's model did not include the costs and benefits of using pembrolizumab as a bridge to transplant because the company did not consider it would be used in this way. 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.

Equalities issues

3.21 It was highlighted during the appraisal consultation that there was potential for the draft recommendation (which did not recommend pembrolizumab for people who have had 2 previous treatments without previous stem cell transplant) to affect older people disproportionately negatively. This is because stem cell transplants are more likely to be unsuitable for older people. The committee noted that suitability of a stem cell transplant was dependent on a person's fitness but also if their condition had responded to chemotherapy, and suitability of transplant

was not defined on the basis of age. The committee concluded that its final recommendation recommended pembrolizumab for people who could and could not have a stem cell transplant and therefore would not disadvantage people who could not have stem cell transplant.

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 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.

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Accreditation