NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pembrolizumab with platinum-based chemotherapy for recurrent, persistent or metastatic cervical cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pembrolizumab with platinum-based chemotherapy 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, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: September 2022

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 with platinum-based chemotherapy 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: 26 October 2022

Second appraisal committee meeting: 8 November 2022

Details of membership of the appraisal committee are given in section 4.

1 Recommendations

1.1 Pembrolizumab plus chemotherapy with or without bevacizumab is not recommended, within its marketing authorisation, for treating persistent, recurrent, or metastatic cervical cancer in adults whose tumours express programmed cell death ligand 1 (PD-L1) with a combined positive score (CPS) of at least 1.

1.2 This recommendation is not intended to affect treatment with pembrolizumab plus chemotherapy with or without bevacizumab 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.

Why the committee made these recommendations

Standard care for persistent, recurrent, or metastatic cervical cancer is usually platinum chemotherapy (cisplatin or carboplatin) and paclitaxel with or without bevacizumab. Clinical trial evidence shows that if people have pembrolizumab plus chemotherapy with or without bevacizumab it takes longer for their cancer to get worse. In the trial period, benefits in survival are also seen.

The cost effectiveness is uncertain. For people having pembrolizumab in combination with chemotherapy with or without bevacizumab, it is unclear how much longer it takes for their cancer to get worse, or how long they live, compared with those having standard care. It is also uncertain how well the modelled curves fit the trial data and how well they predict long-term survival. Because of the problems with the economic model, it is not possible to confidently estimate the cost effectiveness of pembrolizumab in combination with chemotherapy with or without bevacizumab.

Pembrolizumab in combination with chemotherapy with or without bevacizumab meets NICE's criteria to be considered a life-extending treatment at the end of life. Even so, the cost-effectiveness estimates are highly uncertain and are higher than

what NICE usually considers an acceptable use of NHS resources. It is also not possible to assess the potential for use of pembrolizumab in combination with chemotherapy with or without bevacizumab in the Cancer Drugs Fund without more detailed evaluation. So, pembrolizumab in combination with chemotherapy with or without bevacizumab is not recommended for routine use and cannot be recommended for use in the Cancer Drugs Fund.

2 Information about pembrolizumab

Marketing authorisation indication/anticipated marketing authorisation indication

2.1 Pembrolizumab (Keytruda, Merck Sharp Dohme), in combination with chemotherapy with or without bevacizumab, is indicated for 'the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express programmed cell death ligand 1 (PD-L1) with a combined positive score (CPS) ≥ 1'.

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 £2,630.00 per 100 mg/4 ml concentrate for solution for infusion vial (excluding VAT; BNF online accessed September 2022).

2.4 The company has a commercial arrangement. This makes pembrolizumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. 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.

Clinical need and treatment pathway

Recurrent, persistent or metastatic cervical cancer has a high disease burden

3.1 Cervical cancer develops when abnormal cells in the cervix lining grow in an uncontrolled way, forming a tumour. Infection with human papillomavirus is associated with the development of cervical cancer. Cervical cancer is defined as recurrent when it has returned after treatment, persistent when it does not respond to treatment, and metastatic when it has spread beyond the cervix to other places in the body. The patient expert explained that people diagnosed with cervical cancer often experience substantial disruption to their quality of life. With a median age of diagnosis of 51 years, many are of working age, with family and dependants. Despite affecting a younger population, prognosis is poor. Median overall survival with standard treatment (cisplatin and paclitaxel with or without bevacizumab) was just 13 months to 17 months in GOG 240, a randomised phase 3 trial done in people with recurrent, persistent or metastatic cervical cancer. The committee concluded that there is a high disease burden for people with recurrent, persistent or metastatic cervical cancer, and that a treatment that can prolong life but also improve quality of survival by management of symptoms would be welcome.

There are limited effective treatment options available for recurrent, persistent or metastatic cervical cancer

3.2 Clinical experts explained that people with recurrent, persistent or metastatic cervical cancer have limited effective treatment options. People

usually have paclitaxel plus either carboplatin or cisplatin, with or without bevacizumab. Bevacizumab is considered suitable if the person has a good disease performance status, no significant comorbidities, and low risk of bowel fistula formation. The scope and company submission noted that bevacizumab was available as an option through the Cancer Drugs Fund, but the Cancer Drugs Fund clinical lead clarified that bevacizumab is now in routine commissioning for this indication. Although NICE's technology appraisal guidance on topotecan for the treatment of recurrent and stage 4B cervical cancer recommends topotecan, it is not frequently used in clinical practice. The main of aim of treatment is to relieve symptoms and improve quality of life, and to extend life if possible. The patient expert explained that people with recurrent, persistent or metastatic cervical cancer may be worried about the limited time they have left with their family, the lack of available treatment options, and the side effects of treatment. The committee recognised that there are limited effective treatment options available for recurrent, persistent or metastatic cervical cancer.

Clinical evidence

Pembrolizumab plus chemotherapy with or without bevacizumab is more effective than chemotherapy with or without bevacizumab but overall survival data is immature

3.3 The clinical evidence was based on KEYNOTE-826, a phase 3, randomised double-blind placebo-controlled trial in people with persistent, recurrent or metastatic cervical cancer. KEYNOTE-826 compared pembrolizumab plus chemotherapy with or without bevacizumab against placebo plus chemotherapy with or without bevacizumab as a first-line therapy. In line with the marketing authorisation, the company submission presented efficacy data for people whose tumours express programmed death cell-ligand 1 (PD-L1) with a combined positive score (CPS) of at least 1. Chemotherapies included in the trial, either with pembrolizumab or placebo, were cisplatin plus paclitaxel or carboplatin plus paclitaxel. In the

CPS of at least 1 population, 63.1% of people had bevacizumab. The interim trial results showed a clinically meaningful and statistically significant benefit for the pembrolizumab group compared with the placebo group for both progression-free survival and overall survival. The hazard ratio for progression-free survival by investigator assessment for the CPS of at least 1 population was 0.62 (95% confidence interval [CI] 0.50 to 0.77). The hazard ratio for overall survival at 24 months for the CPS of at least 1 population was 0.64 (95% CI 0.50 to 0.81). Median overall survival in the CPS of at least 1 population was not reached in the pembrolizumab group and was 16.3 months in the placebo group. The clinical experts considered that, although people selected for inclusion in clinical trials tended to be fitter than those seen in clinical practice, the overall survival outcomes in the placebo group of KEYNOTE-826 were consistent with those previously seen in the GOG 240 trial. The ERG noted that although an overall survival benefit for the pembrolizumab group was likely because of the separation of the Kaplan–Meier curves between the treatment arms, the duration and size of the long-term benefit beyond trial follow up was uncertain. The committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab is more effective than chemotherapy with or without bevacizumab, but overall survival data is still immature.

People with metastatic cervical cancer at initial diagnosis is not a relevant subgroup and decision making includes the whole marketing authorisation population

3.4 In KEYNOTE-826, people with metastatic cervical cancer at initial diagnosis had statistically significant worse outcomes for progression-free survival and overall survival than people with cervical cancer which was not metastatic at initial diagnosis. The ERG noted that the hazard ratios for the subgroup of people with metastases at diagnosis were comparable to those in the subgroup of people with a PD-L1 status of CPS of less than 1 in the trial, who were excluded from the marketing authorisation.

The clinical experts explained that there was no differentiation between people with metastatic cervical cancer at initial diagnosis and people with recurrent cervical cancer in practice. The clinical experts also noted that the proportion of people with metastatic cervical cancer at initial diagnosis in KEYNOTE-826 was higher than they expected in clinical practice. The committee was cautioned against over-interpretation of results for people with metastatic cervical cancer at initial diagnosis because KEYNOTE-826 was not designed or powered to allow for formal testing of the heterogeneity in subgroups. The ERG explained that people in KEYNOTE-826 were stratified by metastatic status at initial diagnosis so this was not an unplanned subgroup. The committee recalled that it does not seek to create subgroups within the marketing authorisation population unless there is clear underpinning evidence. Clinical experts explained that they would offer pembrolizumab treatment to people with cervical cancer which was metastatic at initial diagnosis based on the benefits seen in the overall CPS of at least 1 population. The committee concluded that people with metastatic cervical cancer at initial diagnosis was not a relevant subgroup and so decision making would include the whole population included in the marketing authorisation.

The company's economic model

The company's model may be adequate for decision making but the most appropriate modelling approach may change when further data becomes available from KEYNOTE-826

3.5 The company presented a 3-state Markov state transition model to estimate the cost effectiveness of pembrolizumab plus chemotherapy with or without bevacizumab compared with chemotherapy with or without bevacizumab. The 3 health states were progression-free survival, progressed disease and death. The company explained that Kaplan–Meier data by response status showed that the overall survival seen in the interim analysis was largely driven by people whose disease had not responded to treatment, and that there is not enough overall survival data

for the people whose disease responded. Overall survival was therefore not mature enough to accurately model long-term survival for people whose disease had and had not responded, particularly those with a complete disease response. It suggested that in this case, a state transition model was more accurate than a partitioned survival model, which relies on direct extrapolation of observed overall survival data. The ERG noted the state transition model approach uses a structural link between progression-free survival and overall survival and implies gains in progression-free survival should translate into gains in overall survival. Although the ERG considered the company's evidence was broadly supportive of this assumption, it noted limited evidence was provided to show a validated relationship between progression-free survival and overall survival in this indication. The ERG also questioned the plausibility of the predicted long-term benefits of pembrolizumab in the model, which were heavily dependent on the approach to extrapolating progression-free survival, and were a direct consequence of the structural link between progression-free survival and overall survival imposed by the state transition model. The committee recalled advice by the NICE DSU technical support document 19 that state transition modelling alongside a partitioned survival approach can assist in verifying the plausibility of extrapolations and addressing the uncertainties in the extrapolation period. The committee concluded that although the company's model may be adequate for decision making with the data currently available, when further data becomes available from KEYNOTE-826, the most appropriate modelling approach may change.

It is likely that improvements in progression-free survival are associated with an overall survival benefit

3.6 Overall survival data from KEYNOTE-826 is immature, with the median overall survival not being reached in the pembrolizumab arm in the interim analysis. The cost-effectiveness modelling therefore relied on progression data to inform longer-term mortality extrapolations. The ERG was concerned that the company's economic model predicts an overall

survival benefit that is similar in size to the progression-free survival benefit, and this was unproven. However, the company noted that the overall survival and progression-free survival hazard ratios seen within KEYNOTE-826 are similar (respective point estimates are 0.64 and 0.62 in the CPS of at least 1 population). The committee considered whether gains in progression-free survival would translate into gains in overall survival. The clinical experts explained that there is a lack of treatment options at second line for recurrent, persistent or metastatic cervical cancer which could affect subsequent survival, and non-cancer mortality was unlikely to have a large effect in this population. So, it was likely that the benefit in progression-free survival would be reflected in overall survival. The Cancer Drugs Fund clinical lead agreed that this was biologically plausible and recalled evidence of gains in progression-free survival leading to gains in overall survival in other cancer trials, including cervical cancer. The committee concluded that, based on its earlier conclusion that pembrolizumab improved progression-free survival compared with placebo, it was likely that pembrolizumab also improved overall survival. However, given the immaturity of overall survival data, the level of this benefit is uncertain.

The company's and the ERG's approaches for extrapolating the time to progression and progression-free survival are not reliable for decision making without further justification

3.7 To inform the risk of disease progression or death, the company extrapolated the time to progression and progression-free survival data. The same model type was used for both time to progression and progression-free survival to ensure the model results remained clinically plausible. Model selection was based on; statistical fit, visual fit, the desire for common functional form of models to both arms, the plausibility of hazard assumptions and clinical plausibility of the survival predictions. The company stated that single piece models in which a parametric distribution was fitted to the whole Kaplan–Meier curve had poor visual fit

to the observed data and were unable to appropriately capture what it considered to be an emerging plateau in the observed survival data. The company's base-case model used a 2-piece approach to modelling time to progression and progression-free survival. Kaplan–Meier data from the KEYNOTE-826 trial was used up to 37 weeks, followed by log-logistic parametric survival models fitted to the remaining observed data. Although the ERG agreed with the company that there was some evidence of an emerging plateau in the time to progression and progression-free survival Kaplan–Meier curves for pembrolizumab, it considered there was limited overall survival evidence to support the substantial progression-free survival and overall survival gains modelled by the company. They also considered that the company's 2-piece approach led to an optimistic projection of people achieving long-term survival on pembrolizumab. The ERG preferred to use a 1-piece log-logistic extrapolation for both arms. In response to technical engagement, the company updated their base-case analysis to align with the ERG's preferred 1-piece log-logistic model for the placebo combination but maintained their preference for the 2-piece Kaplan–Meier plus log-logistic model for the pembrolizumab group. The company explained that they considered the ERG's preferred 1-piece log-logistic model for pembrolizumab to be inappropriate because of a very poor visual fit to the observed data. The company also considered that pembrolizumab has a different mechanism of action to the drugs in the placebo group and suggested it may be appropriate to use a separate model type between arms based on criteria described in the NICE Decision Support Unit Technical Support Document 14. The ERG urged caution in the committee accepting different model types between treatment arms as different shaped distributions, which implied that people can follow different patterns of events depending on which treatment they had. The committee recalled differing model types had been presented in previous appraisals and, although needing adequate justification, may be appropriate if it is accepted that the disease course could be different

depending on the treatment received. The committee concluded that the ERG's preferred 1-piece log-logistic extrapolation for time to progression and progression-free survival may be too pessimistic to reflect the pembrolizumab group, and the company's preferred 2-piece approach may be too optimistic. It did not consider either approach reliable for decision making without further justification, which could include exploration of other methods for estimating long-term outcomes.

The company's approach for extrapolating post-progression survival in the model is reasonable

3.8 To inform the risk of death after progression, the company extrapolated the post-progression survival data from KEYNOTE-826. Though the company considered it unnecessary to apply a proportional hazards modelling approach when patient-level data was available for both the intervention and comparator, it decided that the proportional hazards assumption was violated and fitted independent single parametric distributions to model post-progression survival in both treatment arms. The company selected the generalised gamma distribution for the base-case analysis based on statistical and visual fit to the Kaplan–Meier data and the clinical plausibility of long-term extrapolations and hazard functions. It tested the log-normal and log-logistic distributions as well as an assumption of equal post-progression survival based on a generalised gamma distribution fitted to pooled post-progression survival data for both arms from KEYNOTE-826 in scenario analyses. The ERG was concerned that the long tails predicted by the company's preferred models lacked clinical plausibility. The ERG considered the best match to the observed data was the Weibull curve. The ERG further noted that it is uncertain if any benefits of pembrolizumab will persist beyond progression. The ERG therefore preferred a more conservative assumption where no treatment effect is assumed to persist beyond progression. It considered 2 scenarios to explore this uncertainty: a pooled post-progression survival curve using a generalised gamma curve preferred by the company and a pooled post-progression survival curve using a Weibull curve. The ERG applied the

pooled survival curve using the generalised gamma distribution in their preferred analysis. The committee considered that people who have pembrolizumab are likely to have at least a modest benefit in post-progression survival compared with treatment with placebo. It concluded the company's use of 1-piece generalised gamma models to predict post-progression survival and assuming a differential survival benefit across treatment arms with people whose disease progresses on pembrolizumab assumed to have longer post-progression survival was reasonable.

The duration of benefit for pembrolizumab should include an assumption that the treatment effect wanes after stopping treatment

3.9 In KEYNOTE-826, treatment was stopped after about 2 years. A stopping rule was not included in the marketing authorisation, but the company assumed a stopping rule would apply in line with the trial. Before technical engagement, the company assumed that, despite stopping treatment after a maximum of 2 years, the treatment benefit would be maintained for a lifetime horizon. It explained that this was because the unique mode of action of pembrolizumab results in an extended period of benefit after treatment has stopped and KEYNOTE-826 had showed no evidence of treatment benefit decreasing over the 22 month follow up. The ERG highlighted there was no indication-specific evidence to support a sustained treatment effect, and that the overall immaturity of the survival evidence means any such claimed benefit was highly uncertain. After technical engagement, the company updated their base case to include a treatment waning effect from 5 years to 7 years after stopping treatment. It also presented an alternative, more conservative, treatment waning effect scenario from 3 years to 5 years after stopping treatment. The ERG base-case analysis assumed a waning of the treatment effect from 2 years to 5 years after stopping treatment. The committee heard that treatment waning assumptions had been imposed inconsistently in previous appraisals of immunotherapies. It noted a lack of clear evidence and guidance to inform a precise duration of waning effect but recalled that committees had assumed a waning of the treatment effect from 3 years to

5 years after stopping treatment in previous appraisals for pembrolizumab when a stopping rule had applied. The committee concluded that a treatment waning effect from 3 years to 5 years after stopping treatment with a 2-year stopping rule was reasonable for pembrolizumab.

Utility values

Using the health-state approach to estimate utilities is appropriate

3.10 Health-state utilities in the economic model were estimated from health-related quality of life data collected in KEYNOTE-826. The company used 2 methods to estimate utility in the economic model: the time-to-death approach and the health-state approach. The time-to-death approach categorises utility based on the length of time before death. The health-state approach categorises utilities based on the health states in the model (progression-free survival, progressed disease and death). The company's base case used the time-to-death approach. It explained that delays between progression and symptoms, and different progression types, may blur the effect of progression on health-related quality of life. Progression-based methods may be less appropriate when assessing immunotherapies because of patients experiencing pseudo-progression, where the action of treatment is mistaken for disease. The ERG had concerns with the time-to-death approach. It considered the time-to-death approach to sever the link between progression status and health-related quality of life, violating the accepted conclusion that progression status is key driver of health-related quality of life. The ERG noted the clinical plausibility of this was unclear. The ERG favoured the health-state approach, explaining that most of the previous appraisals of immunotherapies had rejected a time-to-death approach. The committee agreed with the ERG that the health-state approach was preferred because of the lack of evidence to suggest that the underling mechanism of utility generation was based on time-to-death rather than progression. The committee also recalled the health-state approach was more consistent with other appraisals in oncology.

End of life

Pembrolizumab combination meets end of life criteria

3.11 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. Median overall survival was not reached in the pembrolizumab arm of KEYNOTE-826 in the presented interim analysis. A mean 2.19-year survival benefit for the pembrolizumab arm compared with the placebo arm was estimated from the company base-case model after technical engagement. The ERG base case also supported a mean survival gain of greater than 3 months. The committee acknowledged that these survival estimations were based on the company and ERG base cases, so there was an element of uncertainty. The committee agreed that the extension to life for people with recurrent, persistent or metastatic cervical cancer who have pembrolizumab plus chemotherapy with or without bevacizumab is likely to be greater than 3 months compared with current treatment. Median overall survival was 16.3 months in the placebo arm of KEYNOTE-826. Mean overall survival for placebo estimated from the company and ERG base-case models after technical engagement was about 25 months. The company noted that in the KEYNOTE-826 trial, 58.3% of people in the placebo arm had died at 24 months. Additionally, the GOG-240 trial indicates that overall survival at 2 years is 28.3% in the chemotherapy only group and 35.3% in the chemotherapy with bevacizumab group. The committee considered the appeal outcome of NICE's technology appraisal guidance on avelumab that 'normally less than 24 months' allowed a committee discretion to apply end of life criteria even if it felt some measures of life expectancy may be over 24 months. Based on the percentage survival at 24 months in KEYNOTE-826, overall survival in the chemotherapy arms of GOG 240 and the observed and modelled medians, the committee concluded that survival is normally less than 24 months for people with current treatment. Therefore, the committee accepted that the end of life criteria had been met.

Cost-effectiveness estimate

Because of the uncertainty an acceptable incremental cost-effectiveness ratio would be very comfortably below £50,000 per quality-adjusted life year gained

3.12 NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, decisions about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because of confidential commercial arrangements for pembrolizumab, bevacizumab, and post-progression therapies, the ICERs are confidential and cannot be reported here.

The committee noted the high level of uncertainty, specifically:

- the lack of a suitable approach for estimating time to progression and progression-free survival
- the uncertainty around the level of benefit pembrolizumab will have on overall survival.

The committee also agreed that the end of life criteria applied to pembrolizumab, which allows it to consider ICERs of up to £50,000 per QALY gained, but given the level of uncertainty the ICER would have to be very comfortably below this to be accepted for routine commissioning.

There is currently no plausible range of cost-effectiveness estimates

3.13 The company's base-case ICER for pembrolizumab with platinum-based chemotherapy compared with the placebo arm was below £50,000 per QALY gained, when commercial arrangements for pembrolizumab and all the comparator and subsequent treatments were included, but the ERG's estimate was considerably higher. The committees preferred assumptions included:

- modelling a differential post-progression survival benefit across treatment arms using one-piece generalised gamma models (see section 3.8)
- including a treatment waning effect from 3 to 5 years after discontinuation of pembrolizumab treatment with a 2-year stopping rule (see section 3.9)
- using the health-state approach to estimate utilities (see section 3.10).

However, the committee recognised that there were uncertainties and potential flaws in both the company's and ERG's approach to estimating time to progression and progression-free survival and this had a substantial effect on the ICER. The committee noted that the ICERs for the presented scenarios were not reflective of their preferred assumptions and were also not low enough for pembrolizumab with platinum-based chemotherapy therapy to be considered a cost-effective use of NHS resources. The committee also recognised the substantial uncertainty in all of the cost-effectiveness estimates and concluded that it could not recommend pembrolizumab plus chemotherapy with or without bevacizumab for routine use.

Cancer Drugs Fund

Pembrolizumab plus chemotherapy with or without bevacizumab does not currently meet the criteria to be included in the Cancer Drugs Fund

3.14 Having concluded that pembrolizumab plus chemotherapy with or without bevacizumab could not be recommended for routine use, the committee then considered if it could be recommended for treating recurrent, persistent or metastatic cervical cancer 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 estimates in the economic model were highly uncertain, based on an assumption that gains in progression-free survival lead to gains in overall survival.
- different extrapolation models for progression-free survival and time to progression were preferred by the company and the ERG yet the committee did not consider either to be entirely reliable.
- KEYNOTE-826 is still ongoing and direct trial data could help reduce uncertainties about overall survival and extrapolation of progression-free survival and time to progression.
- 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 progression-free survival and time to progression means that it is also uncertain if pembrolizumab with platinum-based chemotherapy has plausible potential to be cost effective.

The committee recalled that there is currently no plausible range of cost-effectiveness estimates. It was not possible to assess the potential for use of pembrolizumab plus chemotherapy with or without bevacizumab in the Cancer Drugs Fund. So, pembrolizumab plus chemotherapy with or without bevacizumab cannot currently be recommended for use in the Cancer Drugs Fund.

Other factors

There are no equality issues relevant to the recommendations

3.15 Potential equality issues raised during the appraisal could not be addressed through NICE technology appraisal guidance. The committee concluded that there were no relevant equality issues.

All relevant benefits of the technology were captured in the QALY calculations

3.16 There have been minimal developments made in managing recurrent, persistent or metastatic cervical cancer over the last decade. Pembrolizumab plus chemotherapy with or without bevacizumab provides benefit for people with recurrent, persistent or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS of at least 1. The committee concluded that all relevant benefits of the technology were captured in the QALY calculations.

Conclusion

Pembrolizumab plus chemotherapy with or without bevacizumab is not recommended

3.17 The committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab is not recommended for treating recurrent, persistent or metastatic cervical cancer. This was because of the uncertainties in the evidence and because all of the ICERs were above the range considered to be a cost-effective use of NHS resources when the end of life modifier was applied.

Jane Adam
Chair, appraisal committee
September 2022

4 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.

Rachel Ramsden
Technical lead

Sally Doss
Technical adviser

Thomas Feist
Project manager

ISBN: [to be added at publication]