NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer

1 Recommendations

1.1 Pembrolizumab plus chemotherapy with or without bevacizumab is recommended for use within the Cancer Drugs Fund as an option for treating persistent, recurrent or metastatic cervical cancer in adults whose tumours express PD-L1 with a combined positive score (CPS) of at least 1. It is recommended only if:

- pembrolizumab is stopped at 2 years of uninterrupted treatment, or earlier if disease progresses, and
- the conditions in the managed access agreement for pembrolizumab are followed.

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.

Issue date: March 2023

© NICE 2023. All rights reserved. Subject to Notice of rights.

Why the committee made these recommendations

Standard care for persistent, recurrent or metastatic cervical cancer includes chemotherapy with or without bevacizumab.

Evidence from a clinical trial shows that, if people have pembrolizumab plus chemotherapy with or without bevacizumab, it takes longer for their cancer to get worse than people having standard care. Evidence from this trial also suggests they may live longer. But, it is unclear how much longer it takes for their cancer to get worse, or how long they live, because the trial is ongoing. In this trial, people had pembrolizumab for up to 2 years.

Because of the uncertainty in the clinical trial evidence, the cost-effectiveness estimates are also uncertain. Pembrolizumab plus chemotherapy with or without bevacizumab meets NICE's criteria to be considered a life-extending treatment at the end of life. But, even when taking this into account, some of the likely cost-effectiveness estimates are above what NICE considers an acceptable use of NHS resources. So, pembrolizumab plus chemotherapy with or without bevacizumab cannot be recommended for routine use in the NHS.

Collecting and analysing data from the ongoing clinical trial through the Cancer Drugs Fund may reduce the uncertainty in the evidence. So, pembrolizumab plus chemotherapy with or without bevacizumab is recommended for use in the Cancer Drugs Fund.

2 Information about pembrolizumab

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'.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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 January 2023).

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, 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

Persistent, recurrent 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 persistent when it does not respond to treatment, recurrent when it has returned after 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 population that is typically younger than

© NICE 2023. All rights reserved. Subject to Notice of rights.

often seen with other cancers, 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 persistent, recurrent or metastatic cervical cancer. The committee concluded that there is a high disease burden for people with persistent, recurrent or metastatic cervical cancer, and that a treatment that can prolong life but also improve quality of survival by managing symptoms would be welcome.

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

3.2 Clinical experts explained that people with persistent, recurrent 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 technology appraisal guidance recommends topotecan for treating recurrent and stage 4B cervical cancer, it is not frequently used in clinical practice. The main aim of treatment for persistent, recurrent or metastatic cervical cancer is to relieve symptoms and improve quality of life, and to extend life if possible. The patient expert explained that people with the condition 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 persistent, recurrent or metastatic cervical cancer.

© NICE 2023. All rights reserved. Subject to Notice of rights.

Clinical evidence

Pembrolizumab combination is more effective than placebo combination but overall survival is uncertain in the long term

3.3 The clinical evidence was based on KEYNOTE-826, a phase 3, randomised double-blind placebo-controlled trial in people with recurrent, persistent 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 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 in clinical trials tend to be fitter than those in clinical practice, the overall survival outcomes in the KEYNOTE-826 placebo group were consistent with those previously seen in GOG 240. 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. After the first committee meeting, the committee concluded that, based on the available

© NICE 2023. All rights reserved. Subject to Notice of rights.

data, pembrolizumab plus chemotherapy with or without bevacizumab is more effective than chemotherapy with or without bevacizumab, but overall survival data is still immature. At the second committee meeting, the clinical expert explained that survival beyond 1 year was considered a good outcome for people with persistent, recurrent or metastatic cervical cancer. In KEYNOTE-826 the survival benefit was already considerable though median overall survival had not yet been reached in the pembrolizumab group. Overall survival data from the interim analysis of KEYNOTE-826 was therefore considered by the clinical expert to be insufficient, not immature. The committee concluded that uncertainty remained about long-term survival for the pembrolizumab group.

Decision making includes the whole marketing authorisation population

3.4 In KEYNOTE-826, people with metastatic cervical cancer at initial diagnosis had statistically significantly worse outcomes for progression-free survival and overall survival than people with non-metastatic cervical cancer 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, who were excluded from the marketing authorisation. The clinical experts explained that, in clinical practice, there was no differentiation between people with metastatic cervical cancer at initial diagnosis and people with recurrent cervical cancer. 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 company 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 for

© NICE 2023. All rights reserved. Subject to Notice of rights.

decision making 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 most appropriate modelling approach may change when further data from KEYNOTE-826 is available

3.5 The company presented a 3-state Markov state transition model to estimate the cost effectiveness of pembrolizumab plus chemotherapy compared with chemotherapy (both 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 overall survival in the interim analysis was largely informed by people whose disease had not responded to treatment, and that there was not enough overall survival data for people whose disease responded. Data on 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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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 Decision Support Unit technical support document 19 that states 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 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 persistent, recurrent 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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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, the level of this benefit is uncertain.

The most appropriate approach for extrapolating time to progression and progression-free survival is uncertain

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 1-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 KEYNOTE-826 was used up to 37 weeks, followed by log-logistic parametric survival models fitted to the remaining observed data. 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. But, it considered there was limited overall survival evidence to support the substantial progression-free survival and overall survival gains modelled by the company. It also considered that the company's 2-piece approach led to an optimistic

© NICE 2023. All rights reserved. Subject to Notice of rights.

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 it 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 given the 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. After the first committee meeting, 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. In response to consultation, the company submitted additional analyses using spline-based extrapolation methods and a response-based model to analyse the time to progression and progression-free survival data. The ERG was satisfied that the company had explored the full range of realistic approaches to survival analysis. However, it did not consider that it was possible for the issue to be fully

© NICE 2023. All rights reserved. Subject to Notice of rights.

resolved given the current data limitations and noted that future data cuts of KEYNOTE-826 would contribute to reducing the associated uncertainty. The committee recognised that these additional analyses may address some of the concerns around the company's extrapolation approach but uncertainties remain around the long-term survival projections. It also recognised that the company may not be able to reduce these uncertainties until longer follow-up data is available from KEYNOTE-826. The committee concluded that the company's updated analyses were helpful for decision making, but the results are still highly uncertain.

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. The company considered it unnecessary to apply a proportional hazards modelling approach when patient-level data was available for both the intervention and comparator. But 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 in which no treatment effect is assumed to persist beyond progression. It considered 2 scenarios

© NICE 2023. All rights reserved. Subject to Notice of rights.

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 its 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 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.

It is appropriate to assume that people will have pembrolizumab for up to 2 years

3.9 In KEYNOTE-826, treatment was stopped at about 2 years (35 cycles). A stopping rule was not included in the marketing authorisation, but the company assumed a stopping rule would apply in line with the trial. The committee therefore concluded that limiting treatment with pembrolizumab to 2 years is in line with KEYNOTE-826 evidence.

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

3.10 Before technical engagement the company assumed that, despite stopping pembrolizumab 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 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

© NICE 2023. All rights reserved. Subject to Notice of rights.

updated its base case to include a treatment effect waning from 5 years to 7 years after stopping treatment. It also presented an alternative, more conservative, treatment effect waning 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. At the first committee meeting, the committee heard that treatment effect 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. In response to consultation, the company noted the committee's preference, but maintained that its preferred treatment effect waning assumption from 5 years to 7 years after stopping treatment was an appropriate middle ground between a 3 to 5-year waning period and no waning. At the second committee meeting, the company recalled that there was no evidence of treatment effect waning in multiple 5-year trials of pembrolizumab and so a treatment effect waning from 3 years to 5 years after stopping treatment was conservative. The ERG noted the 3- to 5-year waning period was not conservative but was consistent with previous appraisals. The committee concluded that a treatment effect waning 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

3.11 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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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, when 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 severed 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 previous appraisals of immunotherapies had rejected a time-to-death approach. After the first meeting, the committee agreed with the ERG that the health-state approach was preferred because of the lack of evidence to suggest that the underlying 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 oncology appraisals. In response to consultation, the company acknowledged the committee's preference, and updated its base case to use the health state-based utility values (with a minor correction identified by the company). The ERG was satisfied that the company had updated the model correctly.

End of life

Pembrolizumab combination meets end of life criteria

3.12 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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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's and ERG's 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 standard care. Median overall survival was 16.3 months in the placebo arm of KEYNOTE-826. Mean overall survival for placebo estimated from the company's and ERG's base-case models after technical engagement was about 25 months. The company noted that in KEYNOTE-826, 58.3% of people in the placebo arm had died at 24 months. Additionally, GOG 240 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 having standard care. Therefore, the committee accepted that the end of life criteria had been met.

© NICE 2023. All rights reserved. Subject to Notice of rights.

Cost-effectiveness estimate

Because of the uncertainty the maximum acceptable ICER would be substantially below £50,000 per QALY gained

3.13 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. In response to consultation, the company considered £50,000 per QALY gained to be the appropriate decision-making threshold. This is because it considered there was enough certainty in the appropriateness of the model structure and in the clinical benefit, as well as consideration of additional benefit it said had not been captured in the model (see section 3.17). It said there was a low risk of decision error because the range of plausible ICER scenarios it had produced were at or below the £50,000 per QALY gained threshold. The ERG disagreed that decision uncertainty was small and recalled that KEYNOTE-826 follow-up is limited and much of the modelled incremental benefit associated with

© NICE 2023. All rights reserved. Subject to Notice of rights.

pembrolizumab is in the extrapolated portion of the survival curve. The committee recognised the high unmet need for people with persistent, recurrent or metastatic cervical cancer and that there would be substantive clinical benefits associated with a positive recommendation for the pembrolizumab group but considered these benefits to already be captured by the model. Given the level of uncertainty, the committee concluded that the maximum acceptable ICER for routine commissioning would be substantially below £50,000 per QALY gained.

Pembrolizumab plus chemotherapy with or without bevacizumab is not recommended for routine use

3.14 The committee's preferred assumptions after the first meeting included:

- modelling a differential post-progression survival benefit across treatment arms using 1-piece generalised gamma models (see section 3.8)
- including a treatment effect waning from 3 years to 5 years after discontinuation of pembrolizumab treatment with a 2-year stopping rule (see section 3.10)
- using the health-state approach to estimate utilities (see section 3.11).

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. Because of this, the committee did not consider the company's or the ERG's original base cases to be suitable for decision making. In response to consultation, the company submitted additional analyses for estimating time to progression and progression-free survival to validate its original approach. The ERG explained in the second committee meeting that the company's approach considered the best fit to observed trial data for the pembrolizumab group while the ERG's approach considered the most clinically plausible extrapolation for the comparator arm and then focused on applying the same model type for

© NICE 2023. All rights reserved. Subject to Notice of rights.

the pembrolizumab arm. It acknowledged that its preferred approach may result in very pessimistic estimates of survival for the pembrolizumab arm but it reiterated that long-term outcomes may also not be as optimistic as predicted by the company's preferred approach.

The company's updated base-case ICER for pembrolizumab plus chemotherapy compared with placebo plus chemotherapy (both with or without bevacizumab) was below £50,000 per QALY gained. This was when commercial arrangements for pembrolizumab and all the comparator and subsequent treatments were included. The ERG's estimate was considerably higher. After the second committee meeting, the committee considered analyses including the following assumptions:

- using a 2-piece approach to model time to progression and progression-free survival (see section 3.7)
- several other of the ERG's preferred assumptions outlined in the first committee meeting, that is:
  - ERG model corrections
  - including costs for GP or nurse visits, blood-counts, and thyroid function tests costs
  - including all adverse events of special interest occurring in more than 5% of people
- including the other company-preferred assumptions, outlined above in section 3.14.

The committee concluded that the most plausible ICERs may be within the range usually considered a cost-effective use of NHS resources when the end of life modifier was applied. However, this is associated with high uncertainty, largely because of the insufficiency of trial data to determine the most plausible approach for extrapolating time to progression and progression-free survival. The committee also recalled that, given the level of uncertainty, the maximum acceptable ICER for routine commissioning would be substantially below £50,000 per QALY gained.

© NICE 2023. All rights reserved. Subject to Notice of rights.

The committee therefore 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 is recommended for use in the Cancer Drugs Fund

3.15 The committee considered if pembrolizumab plus chemotherapy with or without bevacizumab 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:

- the company had expressed during the second committee meeting that it thought the Cancer Drugs Fund may be appropriate, but that it considered that it had provided sufficient data for the committee to recommend pembrolizumab plus chemotherapy with or without bevacizumab for routine use.
- 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 but the committee did not consider either to be entirely reliable.
- KEYNOTE-826 is still ongoing and trial data could help reduce uncertainties about overall survival and extrapolation of progression-free survival and time to progression.
- the committee's preferred ICER has plausible potential to be cost effective when the end of life modifier was applied (the cost-effectiveness estimates are confidential and cannot be reported here).

© NICE 2023. All rights reserved. Subject to Notice of rights.

The committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab met the criteria to be considered for inclusion in the Cancer Drugs Fund. It recommended it for use within the Cancer Drugs Fund as an option for persistent, recurrent or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS of at least 1, if the conditions in the managed access agreement are followed.

Other factors

There are no equality issues relevant to the recommendations

3.16 The committee heard the potential equality issues raised during consultation. The company noted that metastatic cervical cancer was more common among people with low socioeconomic status as well as ethnic minority groups and migrants who have low engagement with vaccination and screening programmes. However, issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. Also during consultation, the patient expert submissions highlighted that there was unequal access to pembrolizumab plus chemotherapy with or without bevacizumab for people with private healthcare insurance in comparison to those without. However, NICE's standard approach to economic modelling (the 'reference case') does not compare NHS healthcare with privately funded healthcare. The committee concluded that there were no relevant equality issues.

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

3.17 There have been minimal developments made in managing persistent, recurrent or metastatic cervical cancer over the last decade. Pembrolizumab plus chemotherapy with or without bevacizumab provides benefit for people with persistent, recurrent or metastatic cervical cancer whose tumours express PD-L1 with a CPS of at least 1. In response to consultation, the company noted health-related quality of life of carers and

© NICE 2023. All rights reserved. Subject to Notice of rights.

dependents of people with persistent, recurrent or metastatic cervical cancer had not been included in the economic model. It also explained that, although the utility data was not available, there was likely to be a significant increase in quality of life for people who remained progression-free beyond 2 years. The ERG recalled the lack of precedent for including additional carer benefits in cancer appraisals. It also considered the magnitude of benefit for people surviving beyond 2 years to likely be minor in terms of determining the ICERs. 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 recommended in the Cancer Drugs Fund

3.18 The committee concluded that the most plausible ICERs may be within the range usually considered a cost-effective use of resource when the end of life modifier was applied, but these were associated with high uncertainty. Collecting more evidence may reduce this uncertainty. So, pembrolizumab plus chemotherapy with or without bevacizumab is recommended for use within the Cancer Drugs Fund as an option for treating persistent, recurrent or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS of at least 1.

4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has recurrent, persistent or metastatic cervical cancer and their tumours express PD-L1 with a CPS of at least 1, and the doctor responsible for their care thinks that pembrolizumab plus chemotherapy with or without bevacizumab is the right treatment, it should be available

© NICE 2023. All rights reserved. Subject to Notice of rights.

for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

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 use in the Cancer Drugs Fund, 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. Drugs that are recommended for use in the Cancer Drugs Fund will be funded in line with the terms of their managed access agreement, after the period of interim funding. 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 the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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.

Chair

Radha Todd

Chair, appraisal committee A

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]

© NICE 2023. All rights reserved. Subject to Notice of rights.